EXHIBIT 11

Patent
Attorney's Docket No. 22338-10230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Control Nos.:	**90/007,542** **90/007,859**		Group Art Unit:	3991
Confirmation Nos.:	7585 ('542) 6447 ('859)		Examiner:	B.M. Celsa
Filed:	13 May 2005 23 December 2005	('542) ('859)		
Patent Owner:	Genentech, Inc. and City of Hope			

For: Merged Reexaminations of U.S. Patent No. 6,331,415 (Cabilly *et al.*)

RESPONSE UNDER 37 C.F.R. § 1.550(b)

Mail Stop **Ex Parte Reexam**
COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication responds to the final Office action mailed February 16, 2007, setting a two-month period for response. Owners timely requested an extension of time to respond under 37 C.F.R. § 1.550(c), and in a Decision dated March 21, 2007, the Office granted an extension to May 21, 2007. As this reply is filed within the extended period for response, it is timely.

We believe that no fee is required for this response. Should any fee be required for entry or consideration of this paper, the Director is requested to charge the appropriate amount to our Deposit Account No. 18-1260.

Patent Owners ("Owners") respectfully request reconsideration of the claims in view of the following remarks.

REMARKS

Exhibit List to Response Filed Under 37 C.F.R. § 1.550(b)

-Exhibit A: MedImmune, Inc. v. Genentech, Inc., No. 04-1300/04-1384 (Fed. Cir. Mar. 7, 2007) Order Remanding Case; MedImmune, Inc. v. Genentech, Inc., CV 03-2567 (C.D. Cal. Apr. 12, 2007) Order Setting the Status Conference

-Exhibit B: U.S. Application No. 06/358,414

-Exhibit C: Second Supplemental Examiner's Answer mailed January 11, 1996 for U.S. Application No. 08/165,530

-Exhibit D: Declaration of Geoffrey T. Yarranton filed during prosecution of U.S. Application No. 08/165,530

-Exhibit E: Office Action mailed May 30, 1997 for U.S. Application No. 08/165,530

I. Preliminary Matters

A. Interview Summary

Representatives of Owners participated in an interview with Examiners Celsa, Jones, and Ponnaluri on March 15, 2007. The interview summary form accurately reflects the subject of the discussions between Owners' representative and the representatives of the Office.

B. Decision on Petition

Owners filed a petition under 37 C.F.R. §§ 1.181 and 1.182 on March 6, 2007, requesting that the Office declare a new reexamination or, in the alternative, withdraw the finality of the outstanding Office Action. In a decision mailed on March 21, 2007, the Office dismissed the petition on procedural grounds. The decision indicated the Owners could file a renewed petition under § 1.182 for a "Request for Continued Reexamination," in accord with the interim policies set forth in the notice regarding changes to reexamination practice published at 1292 Off. Gaz. Pat. & Trademark Office 20 (March 1, 2005). Concurrently with this response, Owners are filing a timely renewed petition under § 1.182, as suggested in the March 21, 2007 decision.

C. Information Disclosure Statements

Owners acknowledge the indication that the materials provided in the information disclosure statements filed on December 14, 2007 and January 16, 2007 have been fully considered. A further information disclosure statement accompanies this response.

Owners also note that the Office has determined that the disclosure in U.S. Patent No. 4,642,334 ("the '334 patent") is cumulative to that of U.S. Patent No. 5,840,545 ("the '545 patent"). See February Office Action, pp. 3-4. The '334 patent was considered during the examination of the application that matured into the patent under reexamination. Thus, the Office fully considered the substance of the '334 and '545 patent disclosures in connection with the original examination of the claims of the '415 patent.

D. Withdrawn Rejections

Owners acknowledge and appreciate the decision of the Office to withdraw all previous grounds of rejection imposed on claims 1 to 36. In particular, the Office no longer is maintaining any rejection based on a determination that the term "or" as it appears in one or

more claims of U.S. Patent No. 4,816,567 ("the '567 patent") was used with other than its ordinary meaning (i.e., as referring to alternatives), and not as a "logical or" meaning (i.e., to mean "and/or").

Owners also observe that all outstanding rejections based on the '567 patent; U.S. Patent No. 4,399,216 ("Axel"); Rice et al., Proc. Nat. Acad. Sci. USA 79: 7862 (1982) ("Rice"); Kaplan et al., EP 0 044 722 ("Kaplan"); Accolla, Proc. Nat. Acad. Sci. USA 77: 563-566 (1980) ("Accolla"); Dallas, WO 82/03088 ("Dallas"); Builder, U.S. Patent No. 4,511,502 ("Builder"); Valle et al., Nature, 300: 71-74 (1982) ("Valle 1982"); Valle et al., Nature, 291: 338-340 (1981) ("Valle 1981"); Deacon et al., Biochem. Soc. Trans., 4: 818-20 (1976) ("Deacon"); Ochi et al., Nature, 302: 340-342 (1983) ("Ochi"); and Oi et al., Proc. Nat. Acad. Sci. USA 80: 825-829 (1983) ("Oi"), as imposed in the previous Office Action, were withdrawn:

E. Status of Litigation Involving the '415 Patent

Owners refer the Office to the previous response where litigation involving the '415 patent was described. In addition to that information, Owners note that on January 9, 2007, the Supreme Court issued a decision reversing the decision of the Federal Circuit in MedImmune, Inc. v. Genentech, Inc., 427 F.3d 958, 76 U.S.P.Q.2d 1914 (Fed. Cir. 2005) and remanding it to the lower court. See MedImmune, Inc. v. Genentech, Inc., 127 S.Ct. 764, 81 U.S.P.Q.2d 1225 (2007). The Federal Circuit then issued a nonprecedential order, recalling the mandate, denying Genentech's motion for briefing and argument, and remanding the case to the district court for further proceedings consistent with the Court's opinion. See MedImmune, Inc. v. Genentech, Inc., No. 04-1300/04-1384 (Fed. Cir. Mar. 7, 2007). The district court issued an order setting a status conference for June 4, 2007. See MedImmune, Inc. v. Genentech, Inc., CV 03-2567 (C.D. Cal. Apr. 12, 2007). Copies of the Federal Circuit's order remanding the case to the district court and the district court's order setting the status conference are provided for the convenience of the Office in Exhibit A to this response.

II. Overview of Owners' Response to New Rejections in February 2007 Office Action

The February 2007 Office Action, while acknowledging that certain portions of the earlier rejections on August 16, 2007 must be withdrawn in light of the arguments and clarifications provided by the Owners, introduced new grounds for rejecting all claims in the

'415 patent.[1] Like the earlier rejections, these new rejections are improper. They are premised on a mistaken view of what the cited references would have taught or suggested to a person of ordinary skill in the art as of early April of 1983, and a number of incorrect scientific and legal assumptions. Owners, for the reasons set forth below, respectfully request withdrawal of these new rejections.

In Section III of this response, Owners demonstrate that the rejection of claims 1-7, 9-10, 14-18, 21, and 23-36 of the '415 patent for anticipation under 35 U.S.C. § 102(e) is based on an incorrect interpretation and improper use of the description and claims of the Moore '545 patent, and a failure to properly focus on the disclosure of the one and only Moore application filed prior to the effective filing date of the '415 patent (i.e., U.S. Application Serial No. 06/358,414 ("the '414 application," Exhibit B) to which the '545 patent claims benefit under 35 U.S.C. § 120. This rejection, being improper, must be withdrawn.

In Section IV, Owners explain that the rejection by the Office of claims 1-7, 9-10, 14-21, and 23-36 of the '415 patent pursuant to 35 U.S.C. § 103(a) are again based on this erroneous use and interpretation of the '545 patent, and must be withdrawn.

Finally, Section V examines the four theories of obviousness-type double patenting advanced by the Office in its rejections, and explains why each one is without merit.

III. The Rejection of Claims 1-7, 9-10, 14-18, 21, and 23-36 as Anticipated by the Moore '545 Patent is Improper and Should Be Withdrawn

Claims 1-7, 9-10, 14-18, 21, and 23-36 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the Moore '545 patent. This rejection should be withdrawn because the claims of the Moore '545 patent do not have a § 102(e) date prior to the effective filing date of the '415 patent, and because the specification of the '545 patent does not describe procedures for co-expression of heavy and light chain polypeptides in a single transformed host cell. Accompanying this response, and discussed below, are declarations from four qualified

---

[1] Owners note that the Office offers its views on construction of various terms in the '415 and '567 patent claims at pages 8-9 of the Office Action. These observations are not accurate in several respects. Since these observations are not being made in the context of setting forth rejections (and certain interpretations are repeated later in the Office Action), Owners are electing to respond to the inaccuracies only as they arise in connection with a specific rejection, infra. Owners expressly reserve their right to contest these interpretations in any subsequent proceedings.

scientists who each provide detailed analyses of the Moore '545 patent and the Moore '414 application. These experts have concluded that there is no description of co-expression procedures in the Moore '414 application and that the claims of the '545 patent, as interpreted by the Office, are not described in the originally-filed Moore specification. Owners also discuss below evidence presented to the Office in unrelated proceedings, involving unrelated parties, that likewise demonstrated (apparently to the satisfaction of the Office) that the originally-filed Moore specification does not disclose co-expression of immunoglobulin heavy and light chains in a single host cell.

A. Legal Standards Governing the Effective Date for § 102(e) Prior Art of the Moore '545 Patent

The law is well settled that the prior art effective date under § 102(e) of a patent which claims the benefit under 35 U.S.C. § 120 to one or more earlier filed applications is the filing date of the earlier application (if any) that provides a disclosure of the claimed invention that complies with 35 U.S.C. § 112, first paragraph. In re Wertheim, 646 F.2d 527, 537, 209 U.S.P.Q. 554, 564 (C.C.P.A. 1981); M.P.E.P. § 2136.03(IV).

In Wertheim, the court was asked to address the specific question of the effective prior art date under §§ 102(e)/103 of a patent which made benefit claims to a series of earlier applications under § 120. 646 F.2d at 536, 209 U.S.P.Q. at 563-64. The Office asserted that the issued patent was prior art under §§ 102(e)/103 as of the filing date of the first of these earlier applications. Id. The court reversed, holding that a patent should be entitled to prior art effect under § 102(e) as of the filing date of an earlier application only if the subject matter of the later issued patent claims was disclosed in that earlier application in a manner that would be sufficient under § 112, first paragraph. Id. at 537-39, 209 U.S.P.Q. at 564-65. ("Thus, the determinative question here is whether the invention claimed in the Pfluger patent finds a supporting disclosure in compliance with § 112, as required by § 120, in the 1961 Pfluger I application so as to entitle that invention in the Pfluger patent, as 'prior art,' to the filing date of Pfluger I. Without such support, the invention, and its accompanying disclosure, cannot be regarded as prior art as of that [Pfluger I application] filing date."). The court observed that a contrary outcome would extend the secret prior art doctrine beyond its logical foundation (i.e., that the subject matter patented could be

fairly considered actually disclosed in the earlier application only if the patent claims could have been issued from that earlier application without dependence on information in the later filings). Id. at 537, 209 U.S.P.Q. at 564 ("[W]e will extend the 'secret prior art' doctrine of Milburn and Hazeltine only as far as we are required to do so by logic of those cases.")[2] The Wertheim court then held that the Pfluger patent "cannot be used as a reference under § 102(e) *alone* against the Wertheim invention as of the date of a Pfluger application which does not describe the Wertheim invention, as claimed." Id. That is, the court held that the § 102(e) effective date of the Pfluger patent was limited to the filing date of only those earlier applications that described the subject matter claimed in the Pfluger patent in a manner that met the requirements of 35 U.S.C. § 112, first paragraph.

The written description requirement prevents applicants from using the amendment process to update their disclosures (by claim amendment or amendment of the specification) during their pendency before the Patent Office. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1255, 70 U.S.P.Q.2d 1321, 1326 (Fed. Cir. 2004). If it were "otherwise[,] applicants could add new matter to their disclosures and date them back to their original filing date, thus defeating an accurate accounting of the priority of invention. *See* 35 U.S.C. 132." Id. at 1255, 70 U.S.P.Q.2d at 1326-27. Accordingly, the law is well settled that a patent is entitled to a prior art effective date under § 102(e) as of the filing date of an earlier application to which a benefit claim is made under § 120 only if that earlier application provides a disclosure for the claimed subject matter that fully complies with the requirements of § 112, first paragraph.

The Moore '545 patent issued from U.S. Application Serial No. 08/461,071 ("the '071 application"). That application claims the benefit under 35 U.S.C. § 120 to eight earlier applications.[3] The originating application in this chain, U.S. Application Serial No. 06/358,414,

---

[2] The conceptual justification for giving a U.S. patent prior art status earlier than the date that the contents of the patent become public (so-called "secret prior art") was first articulated in Alexander Milburn Co. v. Davis-Bournonville Co., 270 U.S. (1926).

[3] The '071 application was not described as being a continuation-in-part of any of its predecessor applications. See '545 patent, col. 1, lines 4 to 17. However, the labels used by an applicant in describing the relationships of the predecessor applications are not conclusive as to whether the predecessor applications provide written description support for the later claimed invention. Transco Products Inc. v. Performance Contracting, Inc., 38 F.3d 551, 556, 32 U.S.P.Q.2d 1077, 1080 (Fed. Cir. 1994) ("[N]o matter what term is used to describe a continuing application, that application is entitled to the benefit of the filing date of an earlier application only as to common subject matter.") Thus, what controls for assessing entitlement of one application (or patent

was filed on March 15, 1982. The Moore '414 application is the only one of the applications in the chain filed before the effective filing date of the '415 patent. Thus, in order for the '545 patent claims to be prior art under § 102(e), the '414 application must satisfy, inter alia, the written description requirement of 35 U.S.C. § 112, first paragraph, for these two claims. In re Wertheim, 646 F.2d at 537, 209 U.S.P.Q. at 564. To meet that requirement, the '414 application must contain a written description that reasonably conveys to one of ordinary skill in the art that the inventor possessed the later-claimed subject matter of claims 1 and 2 of the '545 patent. Tronzo v. Biomet, Inc., 156 F.3d 1154, 1158, 47 U.S.P.Q.2d 1829, 1832 (Fed. Cir. 1998). As explained below, it plainly does not.

B. The Written Description of the '414 Application – the Only Application Filed Prior to the Effective Date of the '415 Patent to Which the Moore '545 Patent Claims Benefit Under 35 U.S.C. § 120 – Does Not Describe Co-Expression of Heavy and Light Chain Polypeptides In One Host Cell

According to the Office, the claims of the Moore '545 patent show a host cell and method of making an immunologically functional immunoglobulin fragment that meet the requirements of claims 1-5, 14-18, 21, 23-25, and 33 of the '415 patent.

Assuming that the Office's interpretation of the Moore '545 patent claims is correct (an issue that Owners address in Section III(C) below), those claims are not prior art to the '415 patent. As will be explained below, a person skilled in the art would not find any description within the Moore '414 application of (a) the host cell and process that the Office contends are defined by the two claims of the Moore '545 patent, or (b) any co-expression concepts. This is demonstrated by the analysis provided in the accompanying declarations under 37 C.F.R. § 1.132 of Dr. Sidney Altman, Dr. Steven McKnight, Dr. Michael Botchan, and Dr. Matthew Scott. Each of these experts, as of the effective filing date of the '415 patent, was practicing in the field of the present invention, and enjoys impeccable scientific credentials. Each of these experts has performed a careful scientific analysis of the contents of the '414 application and explains why the '414 application does not describe any procedure for producing within a single host cell two different polypeptides (e.g., corresponding to heavy and light chain sequences of an

---

issued therefrom) to an earlier effective filing date is whether the earlier-filed application meets the requirements of 35 U.S.C. § 112, first paragraph, as to the later-filed application's claimed invention. M.P.E.P. § 201.11(I)(B)). As will be discussed in section III(B), infra, such is not the case between the '071 application and the '414 application.

immunoglobulin). Instead, the experts conclusively demonstrate in their respective declarations that the only procedures reasonably conveyed by the '414 application for producing immunoglobulin light and heavy chain variable domain polypeptides are ones directed to the production of each polypeptide in a separate host cell culture. See Botchan Declaration, ¶¶ 32, 36; McKnight Declaration, ¶¶ 27-31; Scott Declaration, ¶¶ 8, 11; Altman Declaration, ¶¶ 7, 11, 12.

The only process described in the '414 application for producing an rFv binding composition is one where individual light and heavy immunoglobulin variable region polypeptides are produced in separate cell cultures, isolated from the separate cell cultures, and then combined in vitro to form the rFv. This is unequivocally set forth at page 16, lines 24-28 of the '414 application (the '545 patent at col. 10, lines 8-12), where the written description of the '414 application plainly states:

> The resulting construct is then introduced into an appropriate host to provide expression of the heavy or light polypeptide members of the rFv and the polypeptides isolated. The heavy and light polypeptide members of the rFv are then combined in an appropriate medium to form to the rFv.

(emphases added). The "resulting construct" is a plasmid that contains a single DNA insert encoding either a heavy or a light chain variable region polypeptide, not both. See, e.g., McKnight Declaration, ¶¶ 14, 15, 24-25, 27, 45-46, 48; Botchan Declaration, ¶¶ 27, 28, 31-32, 36, 39; Scott Declaration ¶¶ 9, 11; Altman Declaration ¶¶ 11-12.

Similarly, at pages 17-18 (the '545 patent at col. 10, line 56, to col. 11, line 6), the application states:

> Where the light or heavy chain is not secreted, the transformed microorganisms containing the appropriate ds cDNA for either light or heavy chains are grown in liquid cultures and cleared lysates prepared. These lysates are then passed over an immunosorbent affinity column prepared as described above, employing the specific polyclonal antisera. The bound variable regions are eluted from the column with an appropriate denaturing solvent. The eluates from each of the heavy and light chain isolations are pooled, followed by treatment to renature the polypeptides to form L-rFv and H-rFv respectively. For renaturation, the pooled eluates may be dialyzed against appropriate aqueous buffered solutions. The mixture is then further purified by passing over the

> appropriate ligand-affinity column and the bound molecules eluted with an appropriate denaturing solvent.

(emphases added). In this quote, the reference to "lysates" relates to two preparations made by lysing the cells in each culture to recover the polypeptide made by each cell culture (i.e., the L-rFv or the H-rFv). Then, each "lysate" is purified using an immunoaffinity column – each of the immunoaffinity columns produces an "eluate" containing one polypeptide (i.e., by dissociating the bound polypeptide from the column). As the passage explains, these separate eluates are then combined to form the rFv. Thus, this passage provides a clear indication that each cell culture produces only one polypeptide. See, e.g., Scott Declaration, ¶ 11.

This unequivocal indication that the light and heavy variable region polypeptides are to be produced in separate cell cultures and then combined in vitro to form an rFv is reinforced by the entirety of the '414 written description.

- The process starts with cDNA molecules from a cDNA library, which is produced using an mRNA extract from a hybridoma. Botchan Declaration, ¶¶ 11, 12; Scott Declaration, ¶ 12; Altman Declaration, ¶ 11; McKnight Declaration, ¶¶ 10, 19-21; '414 application, p. 5, line 16 – p. 7, line 11. Each mRNA transcript produces one cDNA. Because the immunoglobulin heavy and light chains are encoded by separate genes, and those genes are located on different chromosomes, the cell will never produce a single mRNA transcript containing heavy and light chain sequences. See, e.g., Botchan Declaration, ¶ 11; Altman Declaration, ¶ 11; McKnight Declaration, ¶ 20. As a result, this cDNA library will never contain a single cDNA that encodes both the heavy and the light chain polypeptides.

- The procedures for preparing the "tailored" cDNA encoding only the variable region of a heavy or light chain use cDNAs from the cDNA library. Each cDNA is sequenced and restriction mapped. Subsequent tailoring of the cDNA is performed by starting with a short oligomer that contains a portion of the variable region sequence of one of the immunoglobulin chains, and incorporates a stop codon at the terminus of that variable region. The oligomer is hybridized to the source cDNA from the cDNA library – meaning that the source cDNA becomes the template for the variable region tailored cDNA – and the full variable region sequence is produced as a complement to the source cDNA sequence. This cDNA containing the stop codon is then hybridized to an oligomer containing a start codon, which ultimately produces a ds cDNA containing the variable region sequence bracketed by a start and a stop codon. This process makes it abundantly clear that a sequence only from a heavy or a light chain variable region is contained in each "tailored" cDNA. See, e.g., McKnight Declaration, ¶¶ 21-22; Altman Declaration, ¶ 11; Scott Declaration, ¶ 12; Botchan Declaration, ¶¶ 13, 19-24.

- The tailored cDNA is inserted into a plasmid that contains regulatory elements that will direct the cell to transcribe and translate only one cDNA insert (i.e., the tailored cDNA containing a sequence only of a heavy or a light chain variable region, not both). There is no description or suggestion of any procedure where a genetic construct is produced that contains or will direct a cell to transcribe two different cDNA inserts, either for amplification or expression purposes. See, e.g., Botchan Declaration, ¶¶ 25, 32; McKnight Declaration ¶ 45; Altman Declaration, ¶ 12.

- The single plasmid is then used to transform a bacterial host. There is no discussion of procedures for transforming a single host with two different plasmids or maintaining a cell culture that will contain multiple plasmids. The absence of that information plainly indicates to a person skilled in the art that bacterial clones containing only one plasmid will be produced. Scott Declaration, ¶ 12; Altman Declaration, ¶¶ 11, 12; Botchan Declaration, ¶¶ 13, 16, 31-32, 36, 42; McKnight Declaration, ¶¶ 46, 51. And, as noted above, each plasmid contains only a heavy or a light chain variable region sequence, not both.

- The specification of the '414 application then indicates that the heavy and light chain polypeptides are to be produced in separate cultures, isolated, renatured, and then combined in vitro to yield the rFv binding composition. See, e.g., McKnight Declaration, ¶¶ 11, 14, 15, 42, 63; Altman Declaration, ¶¶ 11, 12; Botchan Declaration, ¶¶ 25-27, 38; Scott Declaration, ¶¶ 9-10; '414 application, p. 16, lines 24-28.

- The example provided in the patent expressly tracks this process of individual chain expression. It indicates that one cDNA insert encoding either the light or the heavy chain variable region polypeptide is inserted into each plasmid (i.e., thereby producing two different plasmids, with each containing one cDNA insert encoding a light or heavy chain variable region). It also indicates that each plasmid is identical but for the cDNA insert. That makes it absolutely clear to those of ordinary skill in the art that the procedures are producing bacterial cell cultures that contain only singly-transformed bacterial clones (i.e., clones that have either the pGM1H or the pGM1L plasmid). See, e.g., Altman Declaration, ¶¶ 11, 12; Botchan Declaration, ¶¶ 25-32; McKnight Declaration, ¶¶ 19-25, 33-39; Scott Declaration, ¶ 12. When these cells are grown, they will express only one polypeptide – either the L-rFv polypeptide or the H-rFv polypeptide. They cannot express both polypeptides because each cell will contain only one plasmid and each plasmid contains only one cDNA insert encoding the light or heavy chain variable region polypeptide.

Even the original claims presented in the '414 application are expressly limited to individual polypeptide expression methods. See, e.g., McKnight Declaration, ¶ 55. The three independent claims in this original application were claims 1, 7, and 20. Claim 1 is directed to production of one polypeptide chain – either the L-rFV or the H-rFV. Claims 7 and 18, by

contrast, are directed to production of an rFv made from the combination of an L-rFv polypeptide and an H-rFv polypeptide. The last two steps of each of these claims (which are expressed identically in each claim) plainly calls for production of the L-rFv and H-rFv polypeptides in separate host cell cultures, and then combination of these separately produced polypeptides in vitro to form the rFv. These steps read:

> transforming a host with said expression vector[4] and growing said host, whereby the light or heavy variable region polypeptides are expressed; and
>
> combining said light and heavy region polypeptides to form said rFv.

These claims also expressly refer to the cDNA library as being the source of the cDNA used to produce the tailored cDNA encoding either variable region polypeptide, use of hybridization and restriction mapping techniques, and otherwise follow the procedures outlined in the specification. Those procedures result in one cDNA per host cell.

As the declarations of Drs. Altman, McKnight, Botchan, and Scott each explain, the procedures set forth in the '414 application plainly call for the individual production of each variable region polypeptide in a separate host cell culture, and at no point involve production of a host cell that contains cDNA sequences (or a single cDNA sequence) encoding both the light and heavy chain variable region polypeptides. These declarations are conclusive evidence demonstrating that there is no written description support in the '414 application for insertion of two different polypeptide sequences into a single host cell, or for procedures that are designed or intended to produce light and heavy chain variable region polypeptides in a single host cell. It follows then that claims 1 and 2 of the '545 patent, as interpreted by the Office, do not enjoy a priority date under 35 U.S.C. § 120 that predates the filing of the application that matured into the '415 patent.

C. The Office is Incorrectly Interpreting the Claims of the '545 Patent as Requiring Co-Expression of Heavy and Light Chains In One Host Cell

Owners dispute the Office's conclusion that claims 1 and 2 of the Moore '545 patent require co-expression of heavy and light chain polypeptides in a single host cell. There is a different claim interpretation that should be given to those claims that is consistent with the rest

---

[4] This expression vector contains only one cDNA according to the preceding steps of the respective claim (i.e., a cDNA encoding either a light or a heavy chain variable region polypeptide, not both).

of the '545 patent specification. The ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention. Phillips v. AWH Corp., 415 F.3d 1303, 1313, 75 U.S.P.Q.2d 1321, 1326 (Fed. Cir. 2005) (en banc). The person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification. Id.; M.P.E.P. § 2111.01(III).

The Office maintains that claim 1 of the Moore '545 patent requires a host cell that produces two different polypeptides – a heavy chain variable region polypeptide and a light chain variable region polypeptide. This is based on the Office's reading of the claim term "rFv" as requiring variable region polypeptides corresponding to both the heavy and light chains of a source antibody and the specification allegedly describing a host cell transformed with two separate constructs comprising DNA encoding variable light and heavy chains (col. 10, lines 1-5, col. 23, lines 35-45; col. 24, lines 50-60; col. 11, lines 5-12). See February 2007 Office Action, p. 11.

However, the specification indicates that an rFv binding composition may be composed of two identical polypeptides – either two heavy chain variable region polypeptides or two light chain variable region polypeptides. See, the '545 patent, col. 3, lines 2-5 ("The L- and H-designations will normally mean light and heavy respectively, but in some instances the two chains may be the same and derived from either the light or heavy chain sequences." (emphasis added)). The language employed in claim 1 specifies that the claimed rFv is to contain "two polypeptide chains having substantially the same amino acid sequence of at least a portion of the variable region." (emphases added). The singular references (underlined above) can be read to mean that two identical polypeptides are required by the claim. Such an interpretation is consistent with the cited passage of the '545 patent specification and with how an expert would read the disclosure of the '414 application. See McKnight Declaration, ¶ 40. Moreover, as Drs. Altman, McKnight, Botchan, and Scott explain, the descriptions at col. 5, lines 32-35 and col. 7, lines 39-50 do not describe "a 'host cell' transformed with a single genetic construct . . . encoding variable light and heavy chains" as asserted on page 20 of the February 2007 Office Action. Altman Declaration, ¶¶ 12-14; McKnight Declaration, ¶¶ 45, 46; Botchan Declaration, ¶¶ 36, 42, 43; Scott Declaration, ¶¶ 11, 12.

The Office also contends that claim 2 should be interpreted as requiring co-expression because the specification allegedly describes:

- at col. 1, lines 33-42; col. 3, lines 59-63; and col. 17, lines 4-8, independently expressing in a host, variable heavy and light chain domains lacking constant regions; and

- at col. 10, lines 1-5; col. 23, lines 35-45; col. 24, lines 50-60; and col. 11, lines 5-12, either a single genetic construct or two separate constructs comprising DNA encoding light and heavy variable chains.

However, as Drs. Altman, McKnight, Botchan, and Scott explain, these cited portions of the specification would not be read by one of ordinary skill in the art to describe what the Office asserts is described. Altman Declaration, ¶¶ 11, 12; McKnight Declaration, ¶ 46; Botchan Declaration, ¶¶ 36, 37; Scott Declaration, ¶¶ 11-13.

As was the case with claim 1, the only interpretation of claim 2 of the Moore '545 patent that is consistent with the specification is one which requires production of individual heavy and light immunoglobulin polypeptides in separate host cells. In this respect, Owners note that step (1) of the claim indicates that each heavy and light chain sequence is separately cloned – which means that one cDNA sequence will encode only a heavy chain sequence and the other will encode only a light chain sequence. Step (2) of the claim then specifies that each cDNA sequence is to be tailored to contain only the variable region sequences in each of the heavy or light chains. Step (3) of the claim calls for "inserting the tailored DNA molecules into an expression vector . . . ." Disassociated from the specification, this sentence could be read as requiring either (i) that the two sequences are introduced into a single vector or (ii) that each sequence is inserted into its own expression vector. See, e.g., McKnight Declaration, ¶¶ 24, 50-51. Plainly, however, only the latter concept is described in the specification of the Moore '545 patent, as is evident from the expert declarations of Drs. Altman, McKnight, Botchan, and Scott. See Altman Declaration, ¶¶ 11, 12; McKnight Declaration, ¶¶ 48, 51, 52; Botchan Declaration, ¶¶ 36, 37; Scott Declaration, ¶ 12.[5] Finally, step (4) of claim 2 calls for transforming "the host cell with the expression vector and growing the host cell, whereby the light and heavy variable

[5] These experts have focused on explaining the description in the '414 application which is the disclosure to which the '545 patent claims benefit. Thus, the experts' positions as to what is described by the '414 application necessarily translates to what is (or is not) described by the '545 patent specification.

region polypeptides are expressed and associate to form an rFv . . . ." Again, like step (3), the only reading of this clause that is consistent with the written description of the '545 patent is one where each cell is transformed with one vector that contains cDNA encoding only one polypeptide, where separate host cell cultures produce the heavy and light chain variable region polypeptides, and where these separately produced chains are combined after they have been isolated and purified to form the rFv.

D. Another Expert Independently Concluded In 1996 That the Specification of the '545 Patent Does Not Describe Co-Expression

Owners observe that, in proceedings involving an application unrelated to the present reexamination and patent, another expert came to the same conclusion as Owners do here regarding the description and teachings of the disclosure of the Moore '545 patent (other than its claims).[6] U.S. Patent Application No. 08/165,530 to Winter et al. (an application involving expression of Fv antibody polypeptides, attached as Exhibit C) was rejected over the disclosure in the parent of Moore '545, U.S. Patent No. 4,642,334; ("the '334 patent"). The Moore '334 patent like the '545 patent claims the benefit of the Moore '414 application under 35 U.S.C. § 120.

In setting forth the rejection, the Office maintained that the '334 patent described co-expression of heavy and light chain fragments in one host cell. Specifically, it stated "that one can introduce in to an appropriate host, a construct which has within it the appropriate heavy and light chain members" as well as "DNA sequence of the heavy chain and the light chains . . . inserted into a pGM1 plasmid and result in plasmids pGM1H ... and pGM1L," which contain light and heavy chains and "which are both subsequently used to transform *E. coli* HB101 cells." See Winter '530 application, Second Supplemental Examiner's Answer dated January 11, 1996 (Paper No. 25), p. 2, lines 12-14, p. 3, lines 6-10.

---

[6] Owners note that the Office again asserts it is entitled to disregard its past determinations that co-expression of heavy and light chains in a single host cell (e.g., the '415 patent claims) was patentable over the concept (as reflected in the '567 patent claims and in Moore) of expressing one immunoglobulin chain in one host cell. See February 2007 Office Action, p. 42. Owners reiterate that this is improper, as argued previously. See reply filed November 25, 2005, at pp. 13-15; reply filed October 30, 2006, at pp. 6-8. Owners also note that the substantive determinations of the Office even in unrelated applications (such as the now-cited Winter '530 application) conflict with its present determinations.

The applicants addressed the Office's arguments concerning the supposed disclosure of a co-expression system in Moore '334 by presenting a declaration under 37 C.F.R. § 1.132 reflecting the expert opinions of Dr. Geoffrey Yarranton, then the Director of Research of Celltech Ltd. See Declaration C filed as part of Paper No. 27 filed April 3, 1996. Dr. Yarranton analyzed the common disclosure of the Moore '334 and '545 patents (corresponding to the contents of the '414 application) and concluded that there is no description in this common disclosure of co-expression concepts. As Dr. Yarranton explained:

> 5. I have been asked to comment on the issue of whether Moore *et al.* teaches the expression of heavy and light chains together in a single host cell line or separately in two different host cell lines.
>
> 6. The Examiner asserts at the top of page 3 of the Second Supplemental Examiner Answer that column 24, lines 25 to 35 of Moore *et al.* teaches inserting plasmids for expression of the heavy and light chains into a single host cell. This is clearly not the case. As the Examiner points out, the two plasmids which were produced were derived from the same basic plasmid, pGM1. The only difference is that pGM1H contains the heavy chain coding sequence whereas pGM1L contains the light chain coding sequence. This means that pGM1L and pCM1H [sic] contain the same selectable marker. In order to select a transformed host cell, it is necessary to use a selectable marker. Clearly, if the selectable markers are the same in both plasmids, it will not be possible to differentiate between a single transformed line and a double transformed line. Thus, the fact that the plasmids contain the same selectable marker necessarily means that two separate samples of the host cell line were transformed. ...
>
> 7. It is also pertinent that bacteria generally loose [sic] plasmids unless they provide some survival trait. Generally a recombinant plasmid has on it a gene for a selectable marker such as drug resistance. In order to ensure that the plasmid is retained in the transformed host cells, the host cell is grown in a medium containing the relevant drug. If a host cell were to contain two plasmids both of which had the same drug resistance gene, the host cell will lose one or the other of the plasmids as only one would be required to provide the drug resistance. . . . Moore *et al.* indicates that the plasmids are identical except for the coding sequences and so, even if a doubly transformed cell could have been selected, it would not have remained doubly transformed as one or the other plasmid would have been lost. It is therefore absolutely clear that Moore *et al.* used two samples of the same host cell and transformed one sample with the heavy chain vector and the other sample with the light chain vector.
>
> 7.[sic] . . . This refers to the use of two affinity chromatography columns for separation of the heavy and light chains. ... These affinity columns were then to be used to isolate the individual heavy and light chains. It is only after the individual chains

have been eluted from the affinity chromatography columns that the eluates, containing the individual chains, are pooled.

The rejection was eventually withdrawn with reliance in part on the applicant's arguments relating to coexpression. See Office action mailed May 30, 1997 (Paper No. 35) at ¶¶ 3 and 4, citing applicant's reply filed March 5, 1997 (Paper No. 34) at pages . Subsequently, the application was allowed and issued with claims to recombinant methods of making Fv fragments as U.S. Patent No. 5,965,405.

In view of the additional evidence provided by the Yarranton declaration, it is clear to many different experts in the field that the '414 application (i.e., the portion in common between the '334 and '545 patents) does not describe co-expression of heavy and light chain polypeptides in a single host cell.

E. The '545 Patent – To the Limited Extent It Constitutes Prior Art – Does Not Anticipate the '415 Patent Claims.

The scientific analyses of the Moore '414 application provided by Drs. Altman, McKnight, Botchan, and Scott constitute clear and convincing evidence that there is no written description in that application of a host cell that meets the Office's reading of the requirements of claim 1 of the Moore '545 patent, or of a method that meets the Office's reading of the requirements of claim 2 of the '545 patent. As such, neither of these claimed embodiments are part of, or supported by, the original specification of the '414 application (see section III(C), supra). The effective filing date of the '545 patent claims can be no earlier than the date on which those claims were first introduced in the application by preliminary amendment (i.e., the filing date of the '071 application, which was June 5, 1995).

Additionally, as discussed above, none of the other contents of the Moore '545 patent, which is essentially the same as the Moore '414 application, provide any description of a process, host cell, or vector that would meet any of the requirements of the presently rejected claims of the '415 patent.

Moreover, the Moore '545 patent contains no description of a non-bacterial host cell being used to produce light or heavy chain variable region polypeptides. The passage cited by the Office (i.e., col. 5, lines 47-52 of '545 patent) at best suggests that a yeast cell could be a host cell that could be used to amplify cDNA obtained from a cDNA library. There is no discussion

there or anywhere else in the description, however, of yeast cells being used for expression of polypeptides. The only type of host cells identified as being used for expression in the written description of the '545 patent are bacterial host cells. Altman Declaration, ¶ 12; McKnight Declaration, ¶ 12. As such, the Office is incorrect in stating that the Moore '545 written description describes eukaryotic cells, such as yeast, which produce and secrete functioning rFv.

The references in the Office Action on page 12, to applications of rFv's which involve labeling these molecules with toxins or other agents are not relevant to the claims of the '415 patent, as there is no description of the underlying co-expression procedures or host cells that produce both heavy and light chain polypeptides, which are required by the claims of the '415 patent.

Each of the claims of the '415 patent concern processes which comprise expressing DNA sequences encoding heavy and light chain polypeptides in a single transformed host cell, or a vector or host cell comprising such DNA sequences. Since there is no description of a co-expression process (or of a vector or host cells) that produces heavy and light chain polypeptides anywhere in the specification of the Moore '414 application, the '545 patent disclosure (whose prior art effect under § 102(e) is limited to what is disclosed in the '414 application) cannot anticipate the '415 patent claims under 35 U.S.C. § 102(e). Moreover, as no portion of the '414 application provides written description support for the claims of the '545 patent (interpreted by the Office to require a co-expression process or a host cell that produces heavy and light polypeptides), the claims of the '545 patent are not prior art under § 102(e) to the '415 patent claims. Accordingly, the rejections of claims 1-7, 9-10, 14-18, 21, and 23-36 as being anticipated under § 102(e) by the '545 patent are improper and should be withdrawn.

IV. The Rejection of Claims Based on Obviousness Pursuant to 35 U.S.C. § 103(a) Is Improper

Claims 19 and 20 are rejected as being obvious under 35 U.S.C. § 103(a) in view of the rejection of claims 1-7, 9-10, 14-18, 21, and 23-36 as being anticipated by the '545 patent, and in further view of Axel. In addition, claim 22 is further rejected on the basis of the '545 patent taken in consideration of Accolla.

As explained above, the Moore '545 patent claims are not prior art under 35 U.S.C. § 102(e) to the '415 patent. Consequently, they cannot be considered prior art for purposes of an obviousness analysis under § 103(a). Also as explained above, the Moore '414 application (which is the basis of the asserted March 15, 1982 effective prior art date of the Moore '545 patent) contains no description of procedures where heavy and light chain polypeptides are produced in a single transformed cell. Instead, the entirety of the '414 application is directed to procedures that produce each variable region polypeptide in a separate host cell culture, and then combine these separately produced polypeptides in vitro to yield an rFv. As such, the Office is again incorrect in rejecting claims 1-7, 9-10, 14-18, 21, and 23-36 of the '415 patent taken in view of the Moore '545 patent.

With particular respect to the rejection of claims 19 and 20, reliance on Axel is also misplaced. Axel does not describe any procedure whereby two different proteins of interest are to be expressed along with a selectable marker in a single mammalian host cell. Instead, the procedure described in Axel is a two DNA system: the first DNA encodes a single protein of interest and the second DNA encodes a selectable marker. One of ordinary skill in the art reading the entire disclosure would not read the passing references in Axel to "antibodies" to mean that an antibody tetramer is to be produced by co-expressing the heavy and light chains in one host cell. See, infra, section V(D)(1)(a). As such, Axel does not describe a process wherein both heavy and light chain polypeptides are expressed in a single transformed host cell. Axel is discussed, infra, in section V(D)(1)(a).

Since neither the '545 patent nor Axel describes a procedure that produces heavy and light immunoglobulin chains in a single host cell, these patents, alone or in combination, cannot be viewed as rendering obvious the subsidiary concept of co-expression of heavy and light chain polypeptides in a single mammalian cell specified in dependent claims 19 and 20 of the '415 patent. Moreover, there is nothing in Axel that would have motivated a person of ordinary skill in the art to alter the one cell-one chain expression procedures described in the '545 patent disclosure to achieve co-expression in a mammalian cell line. As such, the rejection of claims 19 and 20 under § 103 based on the '545 patent, taken in view of Axel, is improper and should be withdrawn.

For similar reasons, claim 22 is not rendered obvious by the combination of the '545 patent with Accolla. Accolla describes production by a hybridoma of an antibody that binds to carcinoembryonic antigen (CEA). As detailed below in Section V(C)(2), there is no discussion anywhere in Accolla of a procedure for producing, through expression of recombinant DNA sequences, the heavy and light chains of an immunoglobulin that binds to CEA. Since the Office's assertion that Accolla would render production of an anti-CEA antibody through co-expression procedures "obvious" rests on its incorrect determination that the underlying co-expression procedures are disclosed in and anticipated by the '545 patent and, thus, anticipate the rejected claims other than claim 22, the premise of the rejection of claim 22 is improper. Accordingly, the rejection of claim 22 based on the '545 patent taken in view of Accolla is improper and should be withdrawn.

V. The Rejections Based on Obviousness-Type Double Patenting Are Improper

A. Summary of the Four Grounds of Rejection for Obviousness-Type Double Patenting

In the February 2007 Office Action, the Office rejected all of the claims of the '415 patent for reasons of "obviousness-type" double patenting over the claims of the '567 patent. It did so based on four different theories, all of which rely, in whole or in part, on the Office's incorrect analysis of the description in the '545 patent.

First, the Office rejects claims 1-7, 9-11, 13-18, 21, and 23-36 of the '415 patent as being unpatentable for obviousness-type double patenting over claims 1-7 of the '567 patent and the '545 patent. February 2007 Office Action, pp. 15-21.

Second, the Office rejects claims 1-7, 9-11, 13-21, and 23-36 for obviousness-type double patenting over claims 1-7 of the '567 patent and the '545 patent, as applied against claims 1-7, 9-11, 13-18, 21, and 23-46, and further in view of Axel as applied against claims 19-20. February 2007 Office Action, pp. 22-24.

Third, the Office rejects claims 1-7, 9-11, 13-18, and 21-36 for obviousness-type double patenting over claims 1-7 of the '567 patent and the '545 patent, as applied against claims 1-7, 9-11, 13-18, 21, and 23-46, and further in view of Accolla as applied against claim 22. February 2007 Office Action, pp. 24-25.

Because each of these three grounds of rejection is predicated on the incorrect analysis of the '545 patent and its claims, each of these rejections is improper and should be withdrawn. For efficiency, these rejections are addressed in section V(C) below.

Finally, the Office imposes rejections based on a finding that all 36 claims of the '415 patent are "obvious" over the claims of the '567 patent, considered in conjunction with Axel, Rice, Kaplan, taken in view of Dallas, taken further in view of any of Deacon, Valle 1981, or Ochi, "alone or, if necessary further in view of" the '545 patent. February 2007 Office Action, pp. 26-36. Owners addressed the deficiencies of rejections premised on the Office's combination of these publications (other than the '545 patent) in previous responses. For reasons set forth in those earlier responses, and additionally in view of the reasons set forth below, the rejection based on these references of the claims of the '415 patent are improper and should be withdrawn.

B. General Issues Regarding the Office's Multiple Bases for Obviousness-Type Double Patenting Rejections

1. Overview of Legal Standards of Obviousness-Type Double Patenting

An obviousness-type double patenting analysis is analogous to the analysis for obviousness under 35 U.S.C. § 103, except that the claim of the earlier patent serves as the basis for the evaluation of obviousness. The reference claim, however, is not considered as "prior art." See M.P.E.P. § 804(II)(B)(1); General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1281, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992); In re Longi, 759 F.2d 887, 892, 225 U.S.P.Q. 645, 648 (Fed. Cir. 1985).

Generally, an obviousness-type double patenting analysis includes three steps. First, the claims in both the earlier and later patents must be construed. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968, 58 U.S.P.Q.2d 1869, 1878 (Fed. Cir. 2001). Second, the differences between the two claims are identified. Id. Third, it must be determined whether the differences in subject matter between the two claims render the claims patentably distinct. Id. This last step requires an analysis according to the framework of Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966). See M.P.E.P. § 804(II)(B)(1); Studiengesellschaft Kohle mbH v. Northern Petrochemical Co., 784 F.2d 351, 355, 228 U.S.P.Q. 837, 840 (Fed. Cir. 1986) (holding of

invalidity reversed because trial court made no findings on Graham factual inquiries to analyze obviousness-type double patenting).

The Graham analysis, as applied in an obviousness-type double patenting setting, thus requires the following factual inquiries:

(A) determine the scope and content of a reference patent claim relative to a claim in the application at issue (or in this case, the patent at issue);

(B) determine the differences between the scope and content of the reference patent claim as determined in (A), and the claim at issue;

(C) determine the level of ordinary skill in the pertinent art; and

(D) evaluate any objective indicia of nonobviousness.

See M.P.E.P. § 804(II)(B)(1) ("The conclusion of obviousness-type double patenting is made in light of these factual determinations."). The Supreme Court most recently reaffirmed the Graham framework in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 U.S.P.Q.2d 1385, 1391 (2007) ("If a court, or patent examiner, conducts this [Graham] analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103.").

Because the evaluation is to be grounded on the Graham framework, the same cautions and considerations relevant to determinations that apply in conventional obviousness determinations under § 103 apply in an obviousness-type double patenting setting. See M.P.E.P. § 804(II)(B)(1) ("[T]he analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination."). For example, one purpose of the Graham framework is "to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." Graham, 383 U.S. at 36, 148 U.S.P.Q. at 474. The Court in KSR recalled the need for a factfinder to be aware "of the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon ex post reasoning[,]" but cautioned against applying this understanding in a manner that would deny "recourse to common sense." KSR, 82 U.S.P.Q.2d at 1397.

An inquiry into whether a teaching, suggestion, or motivation would have led an ordinary person of skill in the art to combine aspects of the prior art to formulate an invention can provide "helpful insight" to the factfinder and promote the important safeguard against hindsight, but it

must not be applied in an overly rigid manner. See KSR, 82 U.S.P.Q.2d at 1396-1397. The question of whether the prior art does provide this motivation must be assessed using the perspective of the person of ordinary skill in the art at the time of the invention.

The Office also must consider factors such as uncertainty and lack of predictability in the field that would have led a person of ordinary skill in the art to conclude that a proposed invention would not be obvious, even if there may be some general suggestion or desire to attempt to produce the invention. See M.P.E.P. § 2145(X)(B); In re Vaeck, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). These factors were emphasized by the Court in KSR, which provided that "a court must ask whether the improvement is more than the predictable use of prior art elements." KSR, 82 U.S.P.Q.2d at 1396 (emphasis added).

As explained below, a review of the prior art references relied upon by the Office in this action, coupled with the testimony of individuals who can provide an accurate description of the perspective and expectations of a person of ordinary skill in the art in this field in early April of 1983, demonstrate the lack of predictability that existed in the field of recombinant expression of polypeptides at the time of the present invention. Predictability in achieving a result specified in a patent claim through assembly of "known" components was a critical element of the Supreme Court's recent KSR decision. Indeed, the KSR decision emphasizes the importance of asking whether or not a particular combination of references would lead to a predictable solution to a problem. See, e.g., KSR, 82 U.S.P.Q.2d at 1397 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." (emphasis added)). In KSR, the Court held that a person of ordinary skill in the art in that case "would have found it obvious to" combine two elements from the prior art to yield the claims at issue in that case, and there was no genuine question as to whether that combination would work, nor anything that would teach away from the combination. KSR, 82 U.S.P.Q.2d at 1399.

As further explained below, a person of ordinary skill in the art, even assuming he would have considered the possibility of combining the series of references cited by the Office in its rejections, would not have considered the co-expression of heavy and light chains of an immunoglobulin in a recombinant host cell to be predictable based on the teachings in those

references in early April of 1983. The information and guidance in the references cited by the Office, and the overall state of the art, left too many significant gaps of knowledge and uncertainty for a person of ordinary skill to have reasonably predicted outcomes, which is a situation very different than that which the Court found to exist in KSR.

2. The Correct Perspective for Evaluating Prior Art is a Person of Ordinary Skill In the Art as of Early April of 1983, and the Declarations Submitted by Owners Provide This Perspective

The opinions in the expert declarations submitted by the Owners, regarding what the cited references would or would not have taught a person of ordinary skill in the art in early April of 1983 (i.e., the time when the parent application of the '415 patent was filed), provide particularly relevant and insightful evidence on the question of "obviousness," and are entitled to substantial deference. The expert declarations are also presented from the point of view of persons of "ordinary creativity," see KSR, 82 U.S.P.Q.2d at 1397, who were aware that one could look to many different types of references to design experiments. The experts each conclude that these references would not have been read or combined in the manner asserted by the Office, and that these references would have left a person of skill in the art at that time with uncertainty that the subject matter of the '415 patent claims predictably could be achieved at the time using the information in these references.

The Office has not accorded the previously submitted declarations the degree of deference to which they are entitled. It has erred by substituting its own speculations and interpretations of these references and the '415 patent disclosure for the well-reasoned analysis and opinions of experts who can provide the view of persons of ordinary skill in the art in early April of 1983. See In re Zeidler, 682 F.2d 961, 967, 215 U.S.P.Q. 490, 494 (C.C.P.A. 1982) (Board committed reversible error in "substitut[ing] its judgment for that of an established expert in the art" to assess obviousness); In re Katzschmann, 347 F.2d 620, 622, 146 U.S.P.Q. 66, 68 (C.C.P.A. 1965) ("We do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skilled in the art. Where, as here, an affidavit states facts which are relevant to the ultimate determination of the legal issue arising under section 103, we think it must be given careful evaluation and properly weighed to determine whether it factually rebuts the bases upon which the examiner has predicated his finding of obviousness."); In re Fay, 347 F.2d 597, 603, 146

U.S.P.Q. 47, 51 (C.C.P.A. 1965) (affidavit of a well-qualified expert in the field of the invention was evidence supporting finding of non-obviousness of appellants' invention by one of ordinary skill in the art where it provided reasoning based on scientific grounds as to why the prior art teachings would not predict the claimed invention) (citing In re Lulek, 305 F.2d 864, 866, 134 U.S.P.Q. 352, 354 (C.C.P.A. 1962)); M.P.E.P. § 716.01 et seq. (declarations submitted to traverse a rejection are entitled to consideration and when declaratory evidence is determined to be unpersuasive, the Office must "specifically explain" its determination).

"Recognizing the difficulty of casting one's mind back to the state of technology at the time the invention was made, courts have long recognized the usefulness of evidence of the contemporaneous attitude toward the asserted invention. A retrospective view of the invention is best gleaned from those who were there at the time." Interconnect v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551(Fed. Cir. 1985). See also In re McKenna, 203 F.2d 717, 720, 97 U.S.P.Q. 348, 350 (C.C.P.A. 1953) ("the courts should resort not only to an attempt to determine whether an applicant's novel feature is within the capacity of a skilled mechanic in the art, but also to the history and underlying state of the art at or about the time of the alleged invention, the occasion for it, the advantages and successes it achieves. . . . Although there are certain obvious shortcomings in ex parte affidavits as proof, it seems to us that such affidavits are clearly one of the few practical methods of presenting a factual record sufficient to form a basis for proper application of the 'history of the art test' in this type of ex parte proceeding." (internal citations omitted)).

Reviewing the prior art accurately is particularly challenging in the present setting, given that the effective filing date of the '415 patent – April 17, 1983 – was almost 25 years ago and the technical field of the '415 patent is one that has advanced very quickly and significantly. Many procedures that were new or unknown as of April 7, 1983 have since become settled and routine in the field of genetic engineering. However, to accurately assess obviousness, including what was known or could have been reasonably expected by a person of ordinary skill in the art as of the effective filing date, it is essential that the Office ignore those subsequent advances and knowledge acquired after April 7, 1983.

In this regard, Owners again direct the attention of the Office to the numerous declarations provided under 37 C.F.R. § 1.132 in this and earlier responses. Each of these

declarants was a person working in the field of the invention in April of 1983. Each provides accurate insights into what a person of ordinary skill in the art would have understood and expected from the cited references, including several declarants who co-authored some of the references relied upon by the Office. Each of these views is supported by an explanation and, where relevant, citations to literature. The testimony of these declarants constitutes evidence the Office must give proper deference to and demonstrates that many of the assumptions, conclusions, and findings that the Office has reached from the cited references are inaccurate or incorrect. See M.P.E.P. § 716.01(c).

3. The Office Ignores Distinctions Between the '567 and '415 Patent Claims Due to an Improper and Incorrect Reading of the '567 Claims and Specification

The Office sets forth certain opinions regarding the requirements of the claims of the '567 and '415 patents at pages 16-19 and 26-29 of the Office Action. These reflect fundamental flaws that flow throughout and distort the remainder of the Office's analysis. By incorrectly minimizing the differences between the '415 claims on the one hand and the '567 patent on the other, the Office has improperly construed what the references it relies upon would have taught or suggested to a person of ordinary skill in the art, and has improperly found obviousness-type double patenting to exist.

The Office specifically identifies only one difference between the independent claims of the '567 and '415 patents (i.e., that the '567 patent "fails to claim the co-expression of light and heavy antibody chains in a single host cell."). See, e.g., February 2007 Office Action, pp. 19, 29. While this is, indeed, an important difference, the Office fails to identify other key differences between the claims, for example:

- First, the '415 claims require the host cell to be transformed with two DNA sequences, a first DNA sequence encoding at least a variable domain of a light immunoglobulin chain, and a second DNA sequence encoding at least the variable domain of a heavy immunoglobulin chain. The '567 claims do not require that a single host cell be transformed with two DNA sequences (see, e.g., step (a), "preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain").

- Second, the '415 claims require that the heavy and light chain polypeptides "be produced as separate molecules in said transformed single host cell" (see step (ii)

of claim 1). Because there is no requirement in the '567 claims for production of more than one immunoglobulin polypeptide, there is no mention, much less a requirement for, production of the heavy and light chain polypeptides as separate molecules in the '567 patent claims in a single host cell.[7]

- Third, the '415 claims require the assembly of the heavy and light chain polypeptides that have been independently produced in the cell into an immunoglobulin molecule or an immunologically functional immunoglobulin fragment (see lines 1-5 and step (ii) of claim 1)[8]. There is no requirement in the '567 claims that the individual recovered chimeric heavy chain, or recovered light chain in final step (e) be assembled into an immunoglobulin molecule or fragment.

See, Owners' First Response (November 25, 2005), pp. 24-25, 28-29, 31, and Tables 2-6 of Exhibit E; Owners' Second Response (October 30, 2006), pp. 16-17, 29-30.

Each of these distinctions between the '415 and '567 patent claims would have been considered significant by a person of ordinary skill in the art as of early April of 1983. For example, as the expert testimony demonstrates, expression of two – rather than one – exogenous DNA sequences (i.e., encoding the light and heavy chain polypeptides) in a single host cell would not have been considered obvious in early April of 1983. See, e.g., Botchan Declaration, ¶¶ 12-33; McKnight Declaration, ¶¶ 23-39. Harris First Declaration, ¶¶ 15-43; Rice First Declaration, ¶¶ 13-17; Harris Second Declaration, ¶¶ 13-28, 33-97; Rice Second Declaration ¶¶ 9-58. Another example relates to the fact that formation of the immunoglobulin tetramer (or functional fragment) would not have been viewed as straightforward, given the structural complexity of tetrameric immunoglobulin molecules compared to other small monomeric polypeptides that had been recombinantly produced by 1983. See, e.g., Harris Second Declaration, ¶¶ 13-18.

---

[7] As the Office has done, Owners have used claim 1 of the '415 patent and claim 1 of the '567 patent for an illustrative comparison of the claims of the two patents. Distinctions exist between these claims and other independent and dependent claims in the two patents, which Owners have previously discussed. See, e.g., First Response, Table 1, and Exhibit E.

[8] Owners also note that the claims of the '415 patent require, inter alia, assembly of an immunoglobulin molecule an immunologically functional immunoglobulin fragment. Dependent claims illustrate that this can also include the requirement that the immunoglobulin molecule or immunoglobulin fragment be produced within the cell and be secreted therefrom, or that this occur outside the cell.

4. The Office Improperly Relies on the Disclosures of the '567 Patent and the Utility of Its Claims to Find a Suggestion or Motivation for Co-Expression Required by the '415 Patent Claims

To advance its obviousness-type double patenting conclusions, the Office improperly reads unclaimed elements into the '567 claims and impermissibly draws from the teachings in the common patent disclosure shared by the '567 and '415 patents. Part of the Office's error stems from the way it has read the clause "having specificity for a particular known antigen" in the '567 patent claims, based on suggestions that it found in the specification. See February 2007 Office Action, pp. 16, 18, 29. The Office also incorrectly states that the '567 patent includes "claims directed to the same statutory subject matter" as the '415 patent, including "recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins) and immuno-globulin products." February 2007 Office Action, pp. 18, 28 (emphasis added).

a. The Disclosure and Teachings of the '567 Patent May Not Be Used to Hold the '415 Claims Unpatentable for Obviousness-Type Double Patenting

It is legally improper for the Office to use the specification of the '567 patent to read into the '567 patent claims unclaimed features or elements that are required by the claims of the '415 patent. The Office also may not use the "teachings" of the common patent specification or the '567 claims to find motivation, guidance, or a suggestion to modify the '567 claims to arrive at the '415 patent claims. When comparing the claims for obviousness-type double patenting purposes, "the [earlier] patent disclosure may not be used as prior art." In re Vogel, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970); see also General Foods Corp., 972 F.2d at 1281, 23 U.S.P.Q.2d at 1846; In re Kaplan, 789 F.2d 1574, 1579, 229 U.S.P.Q. 678, 682 (Fed. Cir. 1986); Chisum, Patents, § 9.03[1][a] (2005).

A patent specification may be employed to interpret the meaning of an unclear claim term or element. If the claim terms are clear, there is no need to resort to the specification for this "definitional" purpose. And certainly, the Office cannot, under the guise of a "definitional" purpose, use the specification to supply missing elements or features not found in the claims of the reference patent, or consult the disclosure to find motivation and guidance to modify the claims of the first patent to yield the claims of the second patent. This is precisely what the

Office is doing when it attempts to insert unrecited claim elements into the '567 patent claims (e.g., that the '567 claims call for production of an immunoglobulin molecule or fragment), and by relying expressly on the teachings and suggestions in the claims and the specification for motivation to modify these '567 claims to yield the '415 patent claims.

In the present case, the '415 patent claim elements of (i) transforming a host cell with DNA sequences encoding heavy and light chain polypeptides, (ii) producing heavy and light immunoglobulin chain polypeptides as separate molecules in a single host cell, and (iii) forming an immunoglobulin molecule or immunologically functional fragment, are plainly not present in the '567 patent claims. The Office has found that these '415 patent claim elements are not required by the '567 patent claims because it has found the '567 patent claims to not require production of heavy and light chains in a single host cell. See February 2007 Office Action, pp. 4-5. As such, the use by the Office of the '567 patent specification to add these elements into the '567 patent claims is improper.

The Office also plainly errs in concluding that the "Cabilly 1 patented method . . . is part of the state of the prior art as of 1983." See February 2007 Office Action, p. 45. Nearly every reported case addressing obviousness-type double patenting states the contrary – that the claims of the reference patent are not prior art. See e.g., General Foods Corp., 972 F.2d at 1281, 23 U.S.P.Q.2d at 1846 (citing In re Braat , 937 F.2d 589, 594 n.5,19 U.S.P.Q.2d 1289,1293 n.5 (Fed. Cir. 1991); Vogel, 422 F.2d at 442, 164 U.S.P.Q. at 622; In re Plank , 399 F.2d 241, 242, 158 U.S.P.Q. 328, 329 (C.C.P.A. 1968); In re Aldrich, 398 F.2d 855, 859, 158 U.S.P.Q. 311, 314 (C.C.P.A. 1968); In re Boylan, 392 F.2d 1017, 1018 n.1, 157 U.S.P.Q. 370, 371 n.1 (C.C.P.A. 1968); In re Braithwaite, 379 F.2d 594, 600 n.4, 154 U.S.P.Q. 29, 34 n.4 (C.C.P.A. 1967); In re Borah, 354 F.2d 1009, 1018, 148 U.S.P.Q. 213, 221 (C.C.P.A. 1966); In re Sutherland, 347 F.2d 1009, 1015, 146 U.S.P.Q. 485, 491 (C.C.P.A. 1965); In re Sarett, 327 F.2d 1005, 1013, 140 U.S.P.Q. 474, 481 (CCPA 1964) (parentheticals omitted). Moreover, logic holds that the claims of the '567 patent cannot be used to establish what was known or what might have been expected by a person of ordinary skill. The claims of the '567 patent, by definition, represent what the inventors invented that was not disclosed in or obvious from the prior art. The prior art applicable to those claims, and the expectations that would be set by that prior art in the mind of

a person of ordinary skill, are the same for the '415 patent, because both the '567 and the '415 patents have the same effective filing date.

Similarly, the express reliance by the Office on the "utility" of inventions claimed in the '567 patent or disclosed in the common patent specification is improper. See February 2007 Office Action, p. 18. In particular, the Office relies on a "preferred" utility of "immunoglobulin assembly" disclosed in the patent specification in formulating the rejection. See February 2007 Office Action, pp. 18, 29. Despite this, the Office argues that it is not improperly importing specification utilities into the claims or relying on the specification for motivation. See February 2007 Office Action, pp. 47-49. Instead, the Office asserts that it is entitled to rely on the "portions of the specification which provide support for the patent claims . . . when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent," by citing In re Vogel (emphasis added). The Office is plainly incorrect in its interpretation of the holding of Vogel.

In Vogel, resort to the specification was made to determine the meaning of the claim terms "meat product" and "pork" (i.e., whether "pork" was included within the definition of "meat product" or not, and to ascertain their physical characteristics). The specification provided definitions of these terms. So equipped, the court then assessed the distinctions between "pork" and "meat product" as these claim terms were used. As the court held in Vogel:

> In considering the question [of obviousness-type double patenting], the patent disclosure may not be used as prior art . . . . This does not mean that the disclosure may not be used at all. As pointed out above, in certain instances it may be used as a dictionary to learn the meaning of terms in a claim. It may also be used as required to answer the second analysis question above. We recognize that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim. A claim is a group of words defining only the boundary of the patent monopoly. It may not describe any physical thing and indeed may encompass physical things not yet dreamed of. How can it be obvious or not obvious to modify a legal boundary? The disclosure, however, sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether that thing has been modified in an obvious manner.

422 F.2d at 441-42, 164 U.S.P.Q. at 622 (emphases added, internal citations omitted). In other words, under Vogel, it is appropriate to consult the specification of a patent to understand the

meaning of claim terms, and to do so by evaluating the attributes of tangible embodiments of the claimed invention described in the specification. This is an objective inquiry (e.g., what are the properties of pork relative to a meat product?). Vogel did not hold that one could also find motivation and suggestions from other portions of the patent disclosure to modify the "thing" being claimed to yield a different thing.

In the present rejections, the Office is not consulting the specification to define claim terms. Instead, the Office is improperly using the teachings in the specification and claims of the '567 patent to find a specific motivation to modify the '567 patent claims to arrive at the '415 patent claims. In particular, the Office asserts that a person of ordinary skill would be motivated to produce assembled immunoglobulins and immunoglobulin fragments that are the subject of the '415 patent claims because of Office's incorrect interpretation of the meaning of the phrase "having specificity for a particular known antigen" used in the '567 claims. See February 2007 Office Action, p. 49.

Initially, as Owners explain below in section IV(B)(4)(b), the fact that the individual chimeric heavy or light chains can be used to produce an immunoglobulin provides no indication or suggestion that the immunoglobulin be produced by co-expressing the light and heavy chains in one host cell. And, the evidence of record demonstrates that individual heavy or light chains had utility other than for assembly into immunoglobulin molecules. See, e.g., Riggs Declaration ¶¶ 19-30. As such, the Office's reliance on the substance of its assertions about the meaning of "having specificity for a particular known antigen" are misplaced and do not even suggest what the Office asserts.

Moreover, the Office is not asserting that the phrase "having specificity for a particular known antigen" is unclear in its meaning. Indeed, the evidence of record plainly establishes that the meaning of this phrase to a person of ordinary skill in the art is clear – it is describing sequences within the variable region of an immunoglobulin heavy or light chain. Harris First Declaration, ¶ 13.

The Office is also not using the specification as contemplated in Vogel to provide a tangible description of the attributes of the claimed heavy or light immunoglobulin chain of the '567 patent claims. Instead, the Office is improperly using the disclosure to find a potential new

use of these individual chains. Specifically, the Office asserts that the language defining properties of the heavy or light chimeric chain is "*suggesting* the use of the Cabilly 1 claimed immunoglobulins for assembly into antibodies . . . ." Id. The Office also asserts that this "interpretation" is "supported by the fact that both the reference Cabilly 1 and instant patent claims encompass both utilities . . . ." Id. Thus, the Office's concluding observation that it "is not improperly importing specification utilities into the claims or relying on the specification for motivation as asserted by the patentee" simply cannot be reconciled with the explicit statements and reasoning of the Office. Id.

The Office's reliance on Geneva Pharmaceuticals, Inc. v. Glaxosmithkline PLC, 329 F.3d 1373, 68 U.S.P.Q.2d 1865 (Fed. Cir. 2003), on pages 18 and 29 of the Office Action, is similarly improper. In Geneva, the Federal Circuit's finding of obviousness-type double patenting turned on the fact that the written description of the earlier patent "discloses a single utility" of a compound, while the later patent "claims nothing more than [the earlier patent's] disclosed utility as a method of using the Fleming compound." Geneva, 329 F.3d at 1386, 68 U.S.P.Q.2d at 1875. The disclosure of one – and only one – utility, was deemed important because "the applicant could only have obtained a patent by disclosing the composition's utility, and 'such disclosure of usefulness did not constitute separate inventions, but an essential part of a single invention.'" Id. (internal citation omitted). In other words, the utility of the claims of the second patent in Geneva was inherently identical to that of the invention claimed in the first patent.

The '567 and '415 patent claims do not present a situation remotely similar to Geneva. Unlike the claims involved in Geneva, the '567 claimed embodiments have utilities entirely unrelated to formation of immunoglobulin molecules.[9] More significantly, the mere fact that one of the utilities for the '567 patent's chimeric heavy or light chains is to produce immunoglobulins says nothing about whether the particular way of producing immunoglobulins that is claimed in the '415 patent (i.e., in one cell through co-expression) would have been obvious to a person of ordinary skill in the art as of April 1983. There is abundant evidence of record establishing that the '567 patent's chimeric heavy and light chains can be assembled into immunoglobulin molecules or immunologically functional fragments other than by co-

expression in one host cell. See, e.g., '415 patent col. 5, lines 7-12; col. 6, lines 35-50; col. 4, lines 33-50; col. 12, lines 17-30 (illustrating assembly of individually produced chains in vitro). Thus, as Owners have demonstrated and supported with evidence, the co-expression of both a light and heavy exogenous DNA sequence in a single host is certainly not "an essential part" of the invention claimed by the '567 patent. There simply is no analogous relationship between the '567 and '415 patent claims as there was between the two patent claims addressed in Geneva. It would be an improper extension of Geneva to apply it to the present facts. Simply stated, the decision in Geneva does not shed any light on the critical factual determination in this case of whether the co-expression of immunoglobulin heavy and light chains as claimed in the '415 patent would have been obvious as of April 1983 to a person of ordinary skill in the art.

b. The Office Continues to Erroneously Construe Terms In the '567 Claims and to Improperly Use the Patent Disclosure to Find "Motivation"

The Office's assertions about the phrase "having specificity for a particular known antigen" in the '567 patent claims, as Owners have previously pointed out, is factually incorrect. As Owners previously explained, the phrase "having specificity for a known antigen" serves to identify the sequence of amino acid residues present in the variable region of the immunoglobulin heavy or light chain polypeptide. Harris First Declaration, ¶¶ 11-14; Harris Second Declaration, ¶ 34.

Owners' explanations are not mere attorney argument. Owners have provided evidence in the form of § 1.132 declarations which explain why the Office's reading of the phrase is not how a person of ordinary skill in the art would have read the phrase in early April of 1983. As explained above in Section V(B)(2), these declarations must be accorded significant weight, and the Office errs when it substitutes its own understanding for that of the experts. For example, as Dr. Harris explained, a person of ordinary skill in the art at that time would:

> . . . have understood this phrase in the '567 patent claims as referring to the amino acid sequences found within the variable domain of the individual light or heavy chain being produced as it is these sequences that determine the specificity of [an] antibody. Such a person would not have

[9] As Dr. Riggs explained, and as the specification of the '567 patent reveals, there are multiple utilities for individual heavy or light chains that stand independently from their use to produce immunoglobulin molecules or functional fragments.

> read these passages in the claims as being a requirement that a functional, antigen-binding immunoglobulin molecule containing heavy and light chains be produced.

Harris Second Declaration ¶ 34; see also Harris First Declaration, ¶ 13.

Despite this clear factual record, the Office takes the position that it is "reasonable to one of ordinary skill in the art to interpret [the phrase 'having specificity for a particular known antigen'] as suggesting the use of the Cabilly 1 claimed immunoglobulins for assembly into antibodies." February 2007 Office Action, p. 49. The Office, thus, appears to take the position that because one application of the individual chains produced by the '567 patent claims is to assemble them into immunoglobulin molecules and fragments, that somehow renders the co-expression requirement of the '415 patent claims as "obvious."

The Office's interpretation is factually incorrect and legally improper.

Initially, as Owners noted, the '415 claims specify a particular way of producing an assembled immunoglobulin molecule or fragment. Even assuming that a person of ordinary skill in the art would recognize the value of the individually produced chains being incorporated into immunoglobulin molecules and fragments, the '567 patent claims would not implicitly or explicitly suggest the co-expression of heavy and light chain encoding DNA sequences in a single transformed host cell to achieve this goal. Indeed, the procedures outlined in the specification for using these individually produced chains to produce immunoglobulin molecules and fragments is distinct from the co-expression procedures specified in the '415 patent claims. See, e.g., '415 patent, col. 14, line 64 – col. 15, line 9 and lines 60-67.

Owners also disagree with the Office's assertion that the specification suggests that, when the chimeric immunoglobulin chains of the '567 patent are assembled into an immunoglobulin, the "prefer[red]" utility is to co-express the DNA sequences in the same cell. The term "chimeric" is a label that can be used the describe the characteristics of one immunoglobulin chain (e.g., a chimeric heavy or a chimeric light chain) or to describe the characteristics of an assembled immunoglobulin (e.g., a chimeric immunoglobulin). The term "chimeric" standing alone, says nothing about whether the two chains should be assembled into an immunoglobulin. In this respect, Owners also disagree with the Office's assertions at pages

46-49, of the Office Action, that Owners, in past responses, have somehow agreed with the views of the Office.[10]

These observations illustrate why the case law so clearly prohibits the use of the specification to support a double patenting rejection. In the case of chimeric immunoglobulins, the utility is referred to by the office is associated with the '415 claims – not the '567 claims, which, as the Office has already found, do not require co-expression of heavy and light chains in one host cell.

The Office is also incorrect in suggesting that the only practical application of the individually produced chains is assembly into intact immunoglobulin molecules or fragments.[11] As Owners previously explained, and as Dr. Riggs pointed out in his declaration, practical uses for individual chain compositions were well known in early April of 1983.[12] For example, a person could practice the process specified in the claims of the '567 patent claims to produce a homogeneous composition of a heavy or light chain polypeptide. Such compositions – previously produced by purifying the immunoglobulins from natural sources (e.g., blood) – had utility in preparing antisera that was highly specific to one or the other immunoglobulin chain. Recombinantly producing the individual chains is an improved and superior process relative to isolation of these individual chain compositions from blood. It also is a utility of the '567 claims that is unique relative to the '415 claimed processes, which yield cell cultures containing mixtures of the heavy and light chains. Indeed, the patent specification itself identifies these

---

[10] At page 48, the Office asserts that, by using "chimeric" to refer to immunoglobulins, in a prior response, means that the Owners and one of its experts are using the term as the Office has asserted. The Office is incorrect. The past responses did not in any way address whether a "chimeric" individual chain must be assembled into an immunoglobulin molecule or immunoglobulin fragment to be "useful." Similarly, the statements referred to by the Office say nothing about how a chimeric immunoglobulin should be produced. These are simply referring to the physical characteristics of the chains of the immunoglobulin.

[11] Owners direct the attention of the Office to the Riggs Declaration, ¶¶ 19-30.

[12] The Office again misconstrues Dr. Riggs' declaration concerning known applications of individual light or heavy chain polypeptide preparations. As Dr. Riggs pointed out, purified individual heavy or light immunoglobulin chain compositions had significant commercial value in early April of 1983, such as in the production of compositions that could be used to raise highly specific antisera with specificity to one of the two antibody chains. Light-chain specific antisera was known to be useful in detecting free immunoglobulin light (kappa) chain polypeptides in fluids isolated from human patients. As Dr. Riggs explained, the presence of these free light chain proteins in the patient's fluids was a known indicator of the condition of multiple myeloma. Dr. Riggs was not suggesting that "non-specific" immunoglobulins discussed in the '567 patent specification have utility in the diagnosis of multiple myeloma, while "specific" immunoglobulins (and their constituent heavy and light chains) do not.

individual chains as being separate embodiments of the inventions. See '567 patent, col. 5, lines 32-36. This independent utility of the '567 claims demonstrates that a person of ordinary skill in the art would not be "compelled," as the Office seems to suggest, to extend the '567 procedures to the same endpoint required by the '415 patent claims.

Simply put, whatever is disclosed in the specification of the '567 patent regarding the utility of the '567 claimed methods, such as potential applications of the individually produced chains, cannot be used as prior art "knowledge" in an obviousness-type double patenting rejection against the '415 claims. The Office may not use the "teachings" of the '567 patent (including the teachings of its claims) to provide a motivation or suggestion to modify the '567 patent claims to arrive at the '415 claims. The Office's reliance on one possible utility of the '567 claims to construe the '567 claims as requiring assembly of individually produced heavy or light immunoglobulin chains into a functional immunoglobulin molecule, thus, is factually inaccurate and legally improper.

5. The Rationale of In re Keller and In re Merck & Co. Can Not Justify the Office's Failure to Consider Multiple Aspects of the Declarant Statements

The Office dismisses many aspects of the § 1.132 declarations of qualified experts on the basis of the decisions in In re Keller, 642 F.2d 413, 208 U.S.P.Q. 871 (C.C.P.A. 1981) and In re Merck & Co., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986). In particular, the Office repeatedly relies on these cases to dismiss aspects of the expert declarations with the argument that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." See, e.g., February 2007 Office Action, pp. 50, 52, 55, 56, 60, 64. As explained in Owners' last response, the treatment that the Office gives to the expert declarations is flawed – both as to its improper reliance on these cases and as a matter of logic.

As previously explained, obviousness under § 103 is based on factual inquiries, including a determination of what each reference actually would have taught a person of ordinary skill at the relevant time and the differences between the prior art and the claimed invention. See M.P.E.P. § 2141(I). Thus, it is altogether proper in rebutting an asserted prima facie case of obviousness to first evaluate references individually to determine whether or not they teach what

the Office says they teach. See In re Wright, 866 F.2d 422, 426, 9 U.S.P.Q.2d 1649, 1652 (Fed. Cir. 1989) (noting that the PTO had taken statements of the prior art reference "wholly out of context and g[ave] them meanings they would not have had to one skilled in the art having no knowledge of appellant's invention, or to anyone else who can read the specification with understanding"); see also In re Rijckaert, 9 F.3d 1531, 1533-34, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993) (evaluating the teachings of the references relied on by the PTO to reject pending application claims under 35 U.S.C. § 103 individually for what they disclosed and reversing the PTO's rejection of the claims because the references failed to teach all limitations of the claims). And, it is proper for Owners to do so before being required to address the combined teachings of each reference with other prior art. It is only from an understanding of what each individual reference teaches to one of ordinary skill in the art that one can determine what that person would understand from their combination, including whether a person of ordinary skill in the art would be inclined to combine the references at all.

In the last response, each of Drs. Harris, Rice, and Colman evaluated the teachings of the prior art – both individually and collectively – to determine what would have been, in fact, taught by those references. See Rice Second Declaration, ¶¶ 38-45; Harris Second Declaration, ¶¶ 48, 67, 70, 78, 86, 97; Colman Declaration, ¶¶ 25, 36. In this response, Drs. Botchan and McKnight perform a similar analysis. Botchan Declaration, ¶¶ 62, 72, 77, 83, 94, 103, 104; McKnight Declaration, ¶¶ 78, 91, 96, 102, 108, 113. Each analyzed both the individual references and the sum of the teachings from the references considered together to determine whether a person of ordinary skill in the art would have considered the claimed inventions to have been obvious from those teachings considered together. In so doing, they provide reasons why the combination of teachings would neither have suggested nor led one of ordinary skill to have a reasonable expectation of success in achieving co-transformation of a single host cell with DNA encoding heavy and light chain polypeptides or co-expression of that DNA to obtain a tetrameric immunoglobulin. Owners, thus, have explained in significant detail why the Office's determinations regarding the prior art are, in several critical respects, flawed.

In the current rejections, the Office has improperly dismissed relevant testimony from qualified experts and substituted its own views, both as to what each reference says and what it might have meant to a person of ordinary skill in early April of 1983. As detailed above in

Section V(B)(2), this failure to give proper evidentiary weight to the expert declarations is clear error. An accurate understanding of that literature demonstrates that the collective teaching of the references in view of the state of the art in early April of 1983 made in Owners' previous response, as well as in the present response, would not have rendered the '415 claims obvious to a person of ordinary skill in the art in early April of 1983.

6. The Office Has Improperly Relied on Testimony of an Interested Third Party, Rather Than Information In Patents or Printed Publications

The Office is permitted to review affidavits and declarations in the course of a reexamination proceeding, but a rejection may not be based on information contained exclusively in such affidavits and declarations. This rule derives from the regulation limiting citations considered for reexaminations to "patents or printed publications" in 37 C.F.R. § 1.552 (see also M.P.E.P. § 2258), and is set forth in M.P.E.P. § 2258(I)(E):

> Affidavits or declarations or other written evidence which explain the contents or pertinent dates of prior art patents or printed publications in more detail may be considered in reexamination, but any rejection must be based upon the prior art patents or printed publications as explained by the affidavits or declarations or other written evidence. The rejection in such circumstances cannot be based on the affidavits or declarations or other written evidence as such, but must be based on the prior art patents or printed publications.

(emphasis added).

The Office contends that the declaration of David Baltimore, containing Dr. Baltimore's personal opinions, supports its determination of obviousness-type double patenting of the '415 patent claims. The critical determination by the Office is found in the following statement:

> Thus, in light of this teaching [from Rice], it would be reasonable for one of ordinary skill in the art to expect that expressing a light and heavy chain of the *same* antigen specificity (e.g. derived from a known antibody) in a competent host would result in the assembly of a functional antibody. See Declaration of David Baltimore submitted by the 3rd party with the 2nd Request for Reexamination.

February 2007 Office Action, p. 53. The only foundation for this conclusion is the opinion of Dr. Baltimore as expressed in his declaration.

As Owners explained in the last response, and as explained below in section V(D)(1)(b), a person of ordinary skill in early April of 1983 would not have shared the opinions expressed by the Office at page 53, or the conclusory opinions of Dr. Baltimore expressed in his declaration. Indeed, Owners submit that, based on what was actually written by Drs. Rice and Baltimore in the Rice paper, even Dr. Baltimore – in April of 1983 – would not have shared the views expressed in the declaration he has submitted in the present reexamination proceeding.

The use of the Baltimore declaration as supporting an expectation of successful assembly of an immunoglobulin in a hypothetical transformed cell also is not an explanation of what the Rice publication is teaching. Instead, it reflects Dr. Baltimore's personal opinions about a hypothetical situation based on an extrapolation from the teachings of Rice. This is plainly an improper use of third party testimony in an ex parte reexamination.

As the Office appears to appreciate, Rice contains no information at all about the hypothetical situation addressed by Dr. Baltimore (i.e., his belief that if one could make a lymphoid cell that produced heavy and light chains having the same antigen-binding specificity from two exogenous DNA sequences encoding heavy and light immunoglobulin chains, the two chains would associate and form functional antibody in the cell). Rice is clearly limited to its analysis of experiments that involved a lymphoid cell transformed with only one exogenous light chain gene. In fact, there is not even a passing reference in Rice to the concept of expressing two exogenous immunoglobulin genes in a single lymphoid cell, much less the idea of what might happen to the expression products of those genes in the cell. Dr. Baltimore also cites no other printed publication or patent to support his personal opinion. Because there is no foundation for the opinion being expressed by Dr. Baltimore in Rice, or in any other publication or patent identified by the Office or by Dr. Baltimore, it is improper for the PTO to rely on this opinion as a basis for imposing or maintaining a rejection in the present ex parte reexamination proceeding.

As discussed further below, the Office also improperly relies on Dr. Baltimore's personal perspectives instead of the perspectives required by the patent law (i.e., the views of a person of ordinary skill in the art as of April of 1983). Dr. Baltimore, a Nobel laureate with skills and experience far beyond most people working in the field of molecular biology in 1983, bears no resemblance to a person of ordinary skill in the art. And nothing in his declaration indicates that he is attempting to provide the perspective of a person of ordinary skill in the art in April of

1983. Instead, Dr. Baltimore offers a simple conclusion of what he believes, stating that what "I and other [sic] working in the field would have expected." Baltimore Declaration, ¶ 5 (emphasis added). A Nobel laureate's conjecture about reasonable expectations cannot be deemed to be representative of the views that would be held by a person of ordinary skill in the art. Studiengesellschaft Kohle mbH v. Dart Indus., Inc., 549 F.Supp. 716, 732, 216 U.S.P.Q. 381, 391 (D. Del. 1982) (holding that Nobel laureate's theorizing about the evolution in Fischer of ethyl aluminum compounds did not represent the application of "ordinary skill in the art of which said subject matter pertains"). This is particularly true when the conclusion is explicitly stated as being just what the Nobel laureate himself would have expected, rather than what individuals of ordinary skill in the art would have believed.

The Office also has improperly equated Dr. Baltimore and Dr. Rice as individuals of "ordinary skill in the art." See February 2007 Office Action, p. 58. ("Both Dr. Rice and Dr. Baltimore clearly qualify as 'one of ordinary skill in the art' and both are authors of the 1982 PNAS article and thus share the same 'unique perspective' regarding the subject matter presented thereto."). Plainly, this cannot be the case. In April of 1983, Dr. Rice was a post-doctoral student working in Dr. Baltimore's lab. By that time, Dr. Baltimore had spent nearly 20 years working as a research scientist and had already been awarded a Nobel Prize for his work. The Office has not contested the evidence submitted by Owners that a person of ordinary skill in the field of the claimed invention would have been an individual with a Ph.D. in molecular biology or a comparable degree, and about two years of post-doctoral or laboratory experience. Accepting this as an accurate definition of the person of ordinary skill in the art, the Office plainly cannot conclude that Dr. Baltimore is such a person.

Moreover, the Office violates fundamental principles of due process when it relies primarily on the unsupported opinions of a third party witness to support an essential assumption of its obviousness-type double patenting determination, especially in light of conflicting evidence presented by qualified experts speaking from the perspective of one of ordinary skill in the art, including the co-author of Rice. In this type of ex parte setting, Owners do not have the opportunity to cross-examine Dr. Baltimore or question the basis for his opinion. Despite this, the Office places greater weight on Dr. Baltimore's conclusory opinion than it gives to the well-reasoned opinions of qualified experts, which are supported by analysis, logic, and information

from the literature. This is particularly egregious in the present proceeding, given that Dr. Baltimore is not an uninterested party. Specifically, as Owners pointed out in the last Response, Dr. Baltimore is a Director of MedImmune, and it was MedImmune acting through a third party that requested ex parte reexamination of the '415 patent on December 23, 2005. In addition, MedImmune currently is in active litigation with Genentech over the '415 patent.[13] Accordingly, Owners respectfully submit that the testimonial evidence of Dr. Baltimore is neither proper for consideration or use by the Office in this proceeding nor persuasive as to the assertions contained within it.

C. The Rejection of Claims 1-7, 9-11, and 13-36 for Obviousness-Type Double Patenting (at Sections 4-6 of the Office Action) Must Be Withdrawn Because It Is Based Primarily on the Office's Misuse and Incorrect Analysis of the Moore '545 Patent

On pages 15-25, the Office rejects claims 1-7, 9-11, 13-18, 21, and 23-36 of the '415 patent for reasons of obviousness-type double patenting over claims 1-7 of the '567 patent, taken in view of the Moore '545 patent. The Office also rejects claims 19-20 of the '415 patent based on its rejection of claims 1-7, 9-11, 13-18, 21, and 23-36, taken further in view of Axel; and claim 22 based on this rejection of claims 1-7, 9-11, 13-18, 21, and 23-36, taken further in view of Accolla.

Initially, Owners note that the Office has not rejected claims 8 and 12 using the rationale based on claims 1-7 of the '567 patent, taken in view of the '545 patent, and taken further in view of Axel or Accolla. This reflects the Office's determination that these claims of the '415 patent are patentably distinct relative to the claims of the '415 patent that were rejected over the '567 patent claims, taken in view of the '545 patent, Axel, and Accolla.

1. The Rejection of Claims 1-7, 9-11, 13-18, 21, and 23-36 Is Improper, As It Can Not Be Supported by the '545 Patent

The rejection of claims 1-7, 9-11, 13-18, 21, and 23-36 is premised on the Office's incorrect analysis of the '545 patent. As explained above, the '545 patent claims are not prior art to the claims of the '415 patent, as these claims are not described in the manner required by 35 U.S.C. § 112, first paragraph, in the only application filed prior to the effective filing date of the

---

[13] See Brief for Petitioners at 48, n. 18, MedImmune, Inc. v. Genentech, Inc., No. 05-608 (S.Ct. filed May 15,

'415 patent claims (i.e., the '414 application). Rejections predicated on the claims of the '545 patent, thus, are improper.

Also, as explained above, the disclosure in the '414 application does not describe procedures for co-expression of heavy and light chain variable region polypeptides in a single host cell. Instead, the disclosure describes procedures that expressly call for expression of the heavy and light chain variable region polypeptides in separate host cells, and formation of the rFv in vitro.

The portions of the '545 patent that can be considered prior art to the '415 patent claims (i.e., the '414 application disclosure) would have provided no motivation to a person of ordinary skill in the art to modify the '567 patent claims to yield the inventions defined by claims 1-7, 9-11, 13-18, 21, and 23-36 of the '415 patent, as the Office asserts. Specifically, since the '414 application expressly describes a procedure which produces individual heavy or light variable region polypeptides in separate host cells, it cannot be considered in any way as being a teaching or suggestion for modifying the procedures of the '567 patent claims to produce two different immunoglobulin proteins in a single transformed host cell. The rationale outlined by the Office at pages 19-21 of the Office Action is grounded entirely on the Office's incorrect analysis of the disclosure in the '414 application, and the conclusion that the claims of the '545 patent are prior art to the '415 patent claims. In particular, since the '414 application does not describe procedures where a genetic construct is produced that contains cDNA inserts encoding light and heavy variable region polypeptides, or procedures where more than one plasmid is used to transform a host cell, the '414 application does not provide any direction or teaching that would lead a person of ordinary skill in the art to modify the single chain expression procedures of the '567 patent claims to yield the co-expression procedures claimed in the rejected '415 patent claims. Since co-expression is not even addressed in the Moore '414 application, there is no basis for the Office to conclude it provides any insight into co-expression.

Moreover, a person of ordinary skill in the art would not have combined the '567 patent claims with the '545 patent as the Office suggests. The '567 patent claims require that the immunoglobulin heavy (or light) chain have "a constant region homologous to the corresponding

---

2006).

constant regions of an antibody of a first mammalian species." In stark contrast, the '545 patent claims require there to be no constant regions from the heavy or light chain polypeptide at all. See the '545 patent, col. 25, line 33. Thus, the skilled person would not have been inclined to combine these two teachings.

Owners also take issue with the unsupported opinions of the Office set forth at page 21 of the Office Action. There, the Office asserts that a person of ordinary skill in the art would have considered the approach of producing an rFv (i.e., a composition made up of polypeptides from the heavy and light variable regions of an antibody) outlined in the '545 patent as "another solution to the problem faced by Moore of in vivo immunogenicity resulting from the use of antibodies comprising constant chains in *in vivo* diagnosis or therapy." This, the Office concludes, would have motivated the person of ordinary skill in the art to "utilize the Moore reference process to make chimeric antibodies (e.g. humanized) as in Cabilly 1 . . . ."

The Office cites no rationale for why a person of ordinary skill in the art, in April of 1983, would have had this opinion. For example, the Office appears to not appreciate that the '545 patent disclosure identifies factors unrelated to in vivo immunogenicity as a reason for producing rFv polypeptides. See, e.g., '545 patent, col. 1, line 42 to col. 2, line 7 (indicating that benefits of rFv include small size relative to whole immunoglobulins, ability to reach areas in the body inaccessible to whole immunoglobulins, etc.). The Office also seems to ignore the explicit and overriding message reflected in the '545 patent that it is desirable to produce antibody-derived polypeptides where the constant regions of the source antibody have been completely excised. And the Office appears to not give any weight to the attributes that would be possessed by chimeric immunoglobulins and fragments that could not be possessed by rFv binding compositions (e.g., inclusion of constant region sequences that play a role in inducing immunological responses).

Owners refer the Office to paragraphs 61 to 64 of the accompanying expert declaration of Dr. McKnight, which provides § 1.132 declaration evidence that a person of ordinary skill in the art would not have had these opinions in early April of 1983.

2. Rejection of Claims 19-20 and 22 Is Not Supported by the Additional References Relied Upon by the Office

For reasons similar to those outlined in section V(C)(1) above, rejection of claims 19-20 and 22 are not supported by the additional combination of the '567 patent claims, in view of the '545 patent, with the disclosures in Axel or Accolla.

Specifically, as explained earlier, Axel does not describe a procedure for producing heavy and light immunoglobulins in a single transformed mammalian cell line. The obviousness rationale articulated by the Office at page 23 of the Office Action is based on its presumption that the '545 patent would have led a person of skill in the art to modify the '567 patent's claimed procedures to co-express heavy and light immunoglobulin chains in a single non-mammalian host cell. This presumption is incorrect for the reasons explained above.

Additionally, the Office asserts that a person of ordinary skill in the art would have been motivated to modify the bacterial production methods outlined in the '545 patent to produce immunoglobulin heavy and light chain variable region sequences in mammalian cell lines based on the disclosures in Axel. The Office suggests that the mammalian nature of an immunoglobulin protein would have made, to a person of ordinary skill in the art, the selection of mammalian host cells prima facie obvious from Axel. See February 2007 Office Action, p. 23.

The Office's conclusions appear to be based on an incorrect analysis of what Axel describes and would have suggested to a person of ordinary skill in the art in early April of 1983. For example, the Office indicates that Axel teaches that one of the advantages of using mammalian cells relative to bacterial cells for production of "proteinaceous materials" is "the ability to use unaltered genes coding for protein precursors which are converted by the eukaryotic cell to the desired protein." February 2007 Office Action, p. 13. Owners observe that neither the reference chimeric immunoglobulin chains of the '567 patent claims, nor the rFv binding compositions disclosed in the '545 patent, use "unaltered genes." Instead, each uses DNA that does not occur naturally. To the extent the Office's prima facie obviousness determination is based on this rationale, it is simply incorrect.

If the Office believes some more generalized motivation would exist to produce mammalian proteins in mammalian cells, Owners refer the Office to the observations of Dr. McKnight, at paragraph 75 of his declaration. As Dr. McKnight points out, a person of ordinary skill in the art would have recognized certain benefits of using bacterial cells to produce mammalian proteins in early April of 1983 (e.g., cost, simplicity, stability of expression systems, etc.) that would have been weighed against the desirability of expressing mammalian proteins in a mammalian cell line. As such, it would not have been prima facie obvious for a person of ordinary skill in the art, in early April of 1983, to use the Axel patent method to modify the procedures outlined in the '545 patent, as the Office asserts.

The Office also asserts that production of an anti-CEA specific antibody would have been obvious based on the '567 patent claims, taken in view of the '545 patent, and taken further in view of Accolla. For the reasons set forth above and in section V(E)(7) below, Owners disagree. The Office's rejection is again based on its incorrect analysis of the '545 patent and its March 15, 1982 disclosure. Since the premise of the Office's rejection based on Accolla is incorrect (i.e., that the '567 patent taken in view of the '545 patent renders claims 1-7, 9-11, 13-18, and 21-36 of the '415 patent unpatentable for obviousness-type double patenting reasons), the rejection of claim 22 is improper and should be withdrawn.

D. The Rejection of Claims 1-36 Based on the '567 Claims, In View of Axel, Rice, or Kaplan, In View of Dallas, Further In View of Deacon, 1981 Valle, or Ochi, and Optionally In View of the '545 Patent is Improper

As in prior Office Actions, claims 1-36 of the '415 patent are rejected for reasons of obviousness-type double patenting based on a combination of many references. The Office grounds its rejection on two principal determinations. For the reasons detailed in the following sections, each of these determinations is erroneous and unsupported by the references. Consequently, the rejection must be withdrawn.

First, the Office states that "[o]ne of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art." February 2007 Office Action, p. 29. Specifically, the Office states that "the *Axel*, *Rice*, and *Kaplan* references taken in view of the *Dallas* reference teaching would provide motivation" to modify the '567

invention "to cotransform a single host with two vectors each containing DNA encoding a light or heavy chain, or to utilize a single vector containing both light and heavy chain DNA in order to transform a host cell to independently express said DNA sequences . . . ." February 2007 Office Action, p. 31.

Second, the Office states that the "prior art provides further motivation to make active antibody with a reasonable expectation of success." February 2007 Office Action, p. 34. The Office cites Deacon/Valle 1982[14] and Valle 1981 (concerning oocytes), and Ochi/Oi (concerning expression of a light chain gene in lymphocyte cells) because these publications, in the opinion of the Office, provide "further motivation" to make active antibody with a reasonable expectation of success. February 2007 Office Action, p. 36.

The Office then cites the '545 patent, stating this reference is cited, "if necessary," relative to the other references.

1. Axel, Rice, and Kaplan, Considered Alone, Together, or In Combination with Dallas, Would Not Provide a Motivation or Suggestion to Modify the '567 Claims to Transform a Host Cell With, and to Express In That Cell, Exogenous DNA Sequences Encoding Both Light and Heavy Immunoglobulin Chains

Axel, Rice, Kaplan and Dallas, considered individually or collectively, do not teach or otherwise provide any motivation to modify the '567 patent's claimed embodiments to independently express, in one transformed host cell, DNA sequences encoding light and heavy chain sequences. Similar to the '567 patent, Axel, Rice, and Kaplan each describe expression of DNA encoding only one exogenous protein of interest in one host cell. See Harris Second Declaration, ¶¶ 48, 66; Rice Second Declaration, ¶ 32; McKnight Declaration, ¶¶ 69, 70, 81, 94; Botchan Declaration, ¶¶ 50, 51, 76, 77. Dallas would not provide a motivation for co-expressing heavy and light immunoglobulin chains in one host cell when it is considered with the teachings of Axel, Rice, and Kaplan. Dallas concerns expression of simple bacterial genes in bacterial cells which remain associated within the transformed bacterial cell, which is necessary for the Dallas transformed cells to function as a vaccine. See Botchan Declaration, ¶¶ 80, 81; McKnight Declaration, ¶¶ 99, 100; Rice Second Declaration, ¶ 42; Harris Second Declaration, ¶¶ 72, 76.

Thus, as the submitted evidence establishes, a person of ordinary skill in the art in early April of 1983 would not have considered the combination of the '567 patent claims and Axel, Rice, and/or Kaplan, alone or in light of the information in Dallas in a manner that the Office asserts. See Botchan Declaration, ¶¶ 82, 83; McKnight Declaration, ¶¶ 101, 102; Rice Second Declaration, ¶ 43; Harris Second Declaration, ¶¶ 78. Finally, the '545 patent does not alter the analysis because, read accurately, the specification discloses nothing about co-expression of immunoglobulin heavy and light chains in a single host cell, and the claims can not be considered prior art.

a. Axel Does Not Describe or Suggest Co-Expression of Heavy and Light Antibody Chains In One Host Cell, or Production of Intact or Assembled Antibodies

Axel does not describe processes for producing more than one protein of interest in a single transformed host cell.[15] See Harris First Declaration, ¶¶ 22-25, Harris Second Declaration, ¶ 38; Botchan Declaration, ¶¶ 50, 51; McKnight Declaration, ¶¶ 69, 70. The procedure outlined in Axel uses two DNA sequences: a DNA I, which encodes the protein of interest (i.e., which is to be isolated from the cell after its production), and a DNA II, which encodes a selectable marker. See Axel abstract. The expression product of DNA II transforms the phenotype of the cell, allowing it to be selected and propagated to the exclusion of other cells in the culture which have not been transformed. Id.

Drs. McKnight and Botchan confirm this interpretation of Axel. Both explain that Axel is designed to produce one desired protein of interest, not two, in one host cell. Botchan Declaration, ¶ 50; McKnight Declaration, ¶¶ 69, 70. They also explain that Axel contains no description of co-expression of two different proteins of interest in one host cell, such as heavy and light chain polypeptides. Botchan Declaration, ¶ 51; McKnight Declaration, ¶¶ 70, 71. Indeed, each observed that the absence of specific guidance in the Axel description on these issues is a clear indication that Axel is not describing procedures where two different proteins of interest are being produced in one host cell. Id.

---

[14] The Office has reiterated its determination that Valle 1982 is cumulative in its teaching to Deacon and that similarly Oi is cumulative to Ochi.

[15] In Axel, the polypeptide that is sought to be isolated from the transformed cells is encoded by DNA I, while a second polypeptide encoded by DNA II is the marker, which is not isolated, as the protein of interest.

Dr. Botchan, for example, explains that Axel goes to some length to discuss certain parameters of the expression process (e.g., ratios of copies of DNA I relative to copies of DNA II) that could maximize the odds of successful transformation with, and expression of, DNA I. Botchan Declaration, ¶ 52. By contrast, he observes, that Axel does not even mention what would be perceived to be similarly significant concepts, such as transformation of one host cell with a DNA that encodes multiple proteins of interest, or the use of a third discrete DNA (e.g., a "DNA III"), in addition to transformation with a DNA I and the marker gene DNA (DNA II). Botchan Declaration, ¶ 53. See also McKnight Declaration, ¶¶ 71, 74. Both experts conclude that if there were some intent in Axel to describe co-expression of heavy and light chains in one host cell, there would have been at least some discussion of variables specific to doing so somewhere in the patent.

It is clear to scientists working in the field of the invention at the relevant time period, and to others familiar with the art and what was known in the art in early April of 1983, that Axel is describing nothing more than what is inherently required by the '567 patent – production and recovery of one polypeptide (i.e., a heavy or a light immunoglobulin chain polypeptide) in one transformed host cell. See Harris Second Declaration, ¶¶ 39, 44, 48; McKnight Declaration ¶¶ 69-71. As such, a person of ordinary skill in the art would not have been motivated by the description in Axel to modify the '567 patent claims to yield the '415 patent's claimed embodiments. Without this motivation and guidance concerning co-expression, Axel provides no support for the Office's subsequent rejection for obviousness-type double patenting of the claims of the '415 patent.

In response to Owners' previous arguments, the Office states that "Axel discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains." February 2007 Office Action, p. 51 (emphasis added). The Office also continues to assert that Axel describes the production of antibodies as "intact (assembled) proteins." Id. at 29-30. The Office then rejects past responses of the Owners for two reasons.

- First, the Office advances its own interpretation of various portions of the Axel description, and concludes that Axel is describing procedures for the expression of DNA sequences encoding two different proteins of interest in a single cell.

- Second, the Office seeks to justify its interpretation of Axel by citing the "presumption of validity" of 35 U.S.C. § 282 and the law governing enablement of printed publications. See February 2007 Office Action, pp. 50-51.

As detailed below the following subsections, neither of these assertions is supported by the evidence of record or the cited law.

i. Clear and Convincing Evidence Supports Owners' Reading of Axel

In response to the August 2006 Office Action, Owners explained that the way the Office was reading cited passages in Axel was scientifically inaccurate. Owners did not merely offer attorney argument regarding this point; they provided § 1.132 declaration evidence from individuals qualified to express the views of a person skilled in the art as of April of 1983. See Harris First Declaration, ¶¶ 21-30; Harris Second Declaration, ¶¶ 35-48. Despite this previously submitted evidence, the Office maintains that Axel is describing procedures where two different proteins of interest are being produced in a single transformed host cell. The Office points to three passages in Axel to support its conclusions.

First, the Office again points to the word "antibodies" as it appears in several locations in Axel, and states that these references mean that Axel necessarily is describing procedures where heavy and light antibody chains are being produced in one host cell. The Office is simply misreading these passages, as the experts have repeatedly explained.

For example, as Dr. Harris explained, the "antibody" references in Axel appear as part of long laundry lists of types of proteins that could be produced using the Axel patent process. Harris Second Declaration, ¶ 42. He pointed to the total absence of any description in Axel of a procedure where two different polypeptides of interest are to be produced through co-expression in one host cell. Harris Second Declaration, ¶¶ 39, 44, 48. He explained that the way the process is outlined in Axel, and the absence of any observations relevant to co-expression of two different polypeptides of interest that form a multimeric protein, led him to conclude that a person skilled in the art would not have interpreted the brief "antibody" references as the Office has (i.e., that they demonstrate that Axel is describing a procedure where the heavy and light chains of an antibody are being produced in a single host cell). This evidence has not been addressed by the Office.

Owners now refer the Office to further evidence in the form of additional § 1.132 declarations of Drs. McKnight and Botchan. For example, as Dr. McKnight explains:

> 67. The Axel patent indicates that the polypeptides that can be produced by its method include antibody polypeptides. I read the word "antibody" as it is used in the Axel patent to mean individual heavy or light chain polypeptides, not assembled antibody tetramers because of the way the Axel patent refers to antibodies – as one of many types of polypeptides that can be produced. See, e.g., Axel at col. 3, lines 31-36.

Similarly, Dr. Botchan observes:

> 55. In the Office Action (Page 13, lines 8-19), the PTO indicates that the Axel patent must be describing production of heavy and light chains of an antibody in one host cell because it lists "antibodies" as one of the proteins that can be produced using the procedure. I disagree. The Axel patent simply lists "antibodies" as one of many types of proteins that can be produced. The way that the patent mentions this does not suggest anything about coexpressing the two antibody chains in one host cell or producing an intact, assembled antibody. In my opinion, a person skilled in this field would read this passing reference to "antibodies" as simply indicating that antibody polypeptides (i.e., heavy or light chains) can be produced by the Axel procedure.

These declarations further establish that a person of ordinary skill in the art, in early 1983, would not have read the passing references in Axel to "antibodies" as indicating that antibody heavy and light chains should be co-expressed in one host cell. See generally McKnight Declaration, ¶¶ 65-78; Botchan Declaration, ¶¶ 48-62. As they indicate, such a person would read these references as indicating that antibody polypeptides are one type of polypeptide that could be produced. McKnight Declaration, ¶ 74; Botchan Declaration, ¶ 55. For example, Dr. McKnight points out that if the Office's reasoning were valid (i.e., that by mentioning "antibodies" Axel is literally describing co-expression of heavy and light chains in a single host cell, as well as production of intact or assembled antibodies), Axel would also be describing production of far more complex proteins. He notes that Axel also refers to "enzymes" as proteins that can be made by the Axel process. Many proteins known in early April of 1983 consisted of many subunits. As Dr. McKnight illustrates, RNA polymerase was a well-known enzyme in early April of 1983. This protein has ten discrete subunits – which would, under the Office's rationale – all be expressed in one host cell. Dr. McKnight suggests that this is a clearly implausible reading of these simple references in Axel. See McKnight Declaration, ¶ 68.

Second, the Office points to the "plural" reference in the abstract of Axel to "gene or genes." February 2007 Office Action, p. 51. Owners previously explained that this is indicating that multiple copies of the same gene are being introduced into the host cell to increase the likelihood and degree of expression of the polypeptide of interest (i.e., encoded by DNA I). Harris Second Declaration, ¶¶ 45, 46. Dr. Harris and, now, Drs. McKnight and Botchan, have explained that this is how a person of ordinary skill in the art, in early April of 1983, would have read the relevant portions of Axel that explain this concept. McKnight Declaration, ¶ 73; Botchan Declaration, ¶ 60.[16]

Finally, the Office asserts that because Axel contains claims to antibodies, this indicates that Axel intended to specifically claim co-expression of intact or assembled antibodies. See February 2007 Office Action, pp. 29-30. The text of the claims does not state anything about whether the antibodies are intact or assembled, or how they might be produced. In other words, there is nothing in the text of the claims suggesting that antibodies are to be produced by co-expression of heavy and light chains in one host cell. See McKnight Declaration, ¶¶ 65, 71, 72, 74, 76, 77; Botchan Declaration, ¶¶ 51, 59, 61; Harris First Declaration, ¶¶ 27, 28; Harris Second Declaration, ¶¶ 44, 47, 48.

Thus, based on the clear and convincing evidence of record, the Office is incorrect in its conclusion that by simply mentioning "antibodies," Axel would have been read by a person of ordinary skill in the art in early April of 1983 as specifically describing production of intact, assembled antibodies through co-expression of heavy and light antibody chains in one transformed host cell. The evidence shows that the Office's strained reading of a handful of words in Axel is plainly inconsistent with how a person of skill would have read Axel in early April of 1983.

---

[16] Indeed, the Axel claims actually reinforces owner's observations regarding the correct interpretation of the term "multiplicity" as it is used in references to "genes" in Axel. Claim 31 specifies a "process for inserting a multiplicity of foreign DNA I molecules corresponding to multiple copies of a gene coding for a proteinaceous material into a suitable eucaryotic cell . . . ." Similarly, claim 54 refers to a "process for generating a multiplicity of foreign DNA I molecules corresponding to multiple copies of a gene in a eucaryotic cell . . . ."

ii. The Presumption of Validity and Enablement Law are Not Implicated

In response to Owners' arguments and the submitted evidence, the Office asserts that "the selection of an antibody as one or more (multiplicity) of the foreign protein(s) encoded by DNA I is a patented embodiment (See Axel patent claims 7, 23, 29, 37, 60 etc.)" February 2007 Office Action, p. 50. The Office then states that "the Axel patent claims enjoy a presumption of validity once issued (see 35 U.S.C. § 282) and a party seeking to invalidate a patent claim must provide 'clear and convincing' evidence of invalidity to overcome this presumption." Id. In essence, the Office's position is that it can rely on the presumption of validity of § 282 to shield its interpretation of the Axel description. This position is not remotely supportable by the "presumption of validity" of § 282.

Owners do not dispute that § 282 imbues an issued patent with a presumption of validity.[17] However, the presumption of validity of the patent cannot be equated to a presumption that the Office has properly interpreted a claim term in an issued patent. Cf. In re Cortright, 165 F.3d 1353, 1359, 49 U.S.P.Q.2d 1464, 1468 (Fed. Cir. 1999) (holding the Board's construction of the claim limitation "restore hair growth" as requiring the hair to be returned to its original state was held to be an incorrect interpretation of the limitation because that interpretation was inconsistent with applicant's disclosure and the disclosure of three patents from analogous arts using the same phrase to require only some increase in hair growth). Rather, the words of a claim "are generally given their ordinary and customary meaning." Phillips, 415 F.3d at 1313, 75 U.S.P.Q.2d at 1326. "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Id.; see also M.P.E.P. § 2111.01(III).

---

[17] The presumption of validity is a procedural device. SSIH Equipment S.A. v. U.S. Int'l Trade Comm'n, 718 F.2d 365, 375, 218 U.S.P.Q. 678, 687 (Fed. Cir. 1983). It places on the challenger of a patent the burden of coming forward with clear and convincing evidence to establish facts which may lead to the conclusion that the patent is invalid. Id. Although not susceptible to precise definition, "clear and convincing" evidence has been described as evidence which produces in the mind of the trier of fact "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Colorado v. New Mexico, 467 U.S. 310, 316 (1983); see also C. McCormick, Evidence § 340, at 796 (2d ed. 1972); Price v. Symsek, 988 F.2d 1187 1191, 26 U.S.P.Q. 2d 1031, 1034 (Fed. Cir. 1993).

There also is no conceivable legal rationale for the Office to assert that the presumption of validity of § 282 shields the Office's interpretation of passages of text in the Axel specification. The Office is attempting to use the presumption of validity to simply defend its interpretation of the word "genes" as used in the abstract of Axel (i.e., that it demonstrates that Axel is describing a process of producing heavy and light antibody chains in a single co-transformed host cell). The presumption of validity cannot be relied upon for this purpose.

The Office also cites In re Rasmussen, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981), for the legal principle that a publication is presumed to be enabled for what is described in it. Like the presumption of validity, the issue of "enablement" of the teachings in Axel is not implicated by Owners' previous or current responses. Instead, Owners' position is that the Office's reading of the cited passages in Axel is simply scientifically inaccurate.

As such, Owners submit that § 282 and the "enablement" standard for assessing publications used as prior art are simply irrelevant to the question of whether the Office has properly interpreted the teachings of Axel. Based on the submitted evidence, Axel simply does not describe co-expression of heavy and light immunoglobulin chains in a single co-transformed host cell and does not describe production in transformed host cells of "assembled or intact" antibodies.

b. Rice Does Not Suggest Production of Exogenous Heavy and Light Chain Genes in a Single Host Cell

The Office maintains that Rice would have motivated a person of ordinary skill, in early April of 1983, to modify the '567 claimed processes to yield co-expression of heavy and light chains in one host cell, as required by the '415 claims. The Office states its conclusion at page 30 that "Rice demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins."

In early April of 1983, one of ordinary skill in the art would not have considered Rice to make co-expression of two exogenous chains in a single host cell obvious, much less address what might happen if one were able to produce exogenous heavy and light chains in a lymphoid cell. As explained by the extensive evidence of record (in the form of § 1.132 declarations and other contemporaneous literature):

- A person of ordinary skill in the art, reading Rice in early April of 1983, would not have equated a showing of (a) expression of one exogenous light chain gene in a lymphoid cell expressing its endogenous heavy chain gene, with (b) a process in which two exogenous immunoglobulin chain genes must be introduced and expressed in a single lymphoid cell. See, e.g., Rice Second Declaration, ¶¶ 27-28; Harris Second Declaration, ¶¶ 61-62; Botchan Declaration, ¶¶ 67-69; McKnight Declaration, ¶¶ 82-83, 90-91.

- Rice describes experiments which used a particular type of lymphoid cell line – one that previously had expressed both exogenous chains, and was continuing its production of the endogenous heavy chain gene. The attributes of the cell line used in Rice facilitated the investigational study being performed in Rice of factors that could affect immunoglobulin gene expression (e.g., Dr. Rice explained that the cell was "poised" to express the introduced light chain gene). See, Rice Second Declaration, ¶ 31. Because of the limited experimental design in Rice, one of ordinary skill in the art would not have considered the teachings in Rice to be broadly applicable. See, e.g., Harris Second Declaration, ¶¶ 57, 59, 61-63; Rice Second Declaration, ¶¶ 15-16; Botchan Declaration, ¶ 68; McKnight Declaration, ¶¶ 87-88.

- Rice contains key observations in it that limit how a person of ordinary skill in the art might have been inclined to extrapolate its showings. See, e.g., Harris Second Declaration, ¶¶ 52-56, 62; Rice Second Declaration, ¶ 20; Botchan Declaration, ¶¶ 66,68-69; McKnight Declaration, ¶¶ 83, 85-86, 90. Indeed, Rice itself points out the need for additional research to answer the questions it identifies as existing that relate to gene expression.

- Rice reflects the prevailing views of a person of ordinary skill in the art concerning expression of immunoglobulin genes in lymphoid cells; namely, that this process was unpredictable, not well understood, and regulated by unknown and uncharacterized factors and processes. See, e.g., McKnight Declaration, ¶ 83.

- Thus, reading Rice, one of ordinary skill in the art in early April of 1983 would have considered that expression of even a single rearranged gene (*i.e.*, isolated from another lymphoid cell) was an uncertain and unpredictable process. See, e.g., Harris Second Declaration, ¶¶ 57-59; Botchan Declaration, ¶ 72; McKnight Declaration, ¶¶ 83-87, 91.

In the interest of efficiency, Owners are not restating the positions expressed in the prior responses regarding the teachings of Rice to a person of ordinary skill in the art in early April of 1983. Owners expressly reserve and maintain these previously expressed positions concerning Rice.

In reaching a contrary conclusion, the Office misstates the actual teachings of Rice and ignores the state of knowledge in the art in early April of 1983. See February 2007 Office

Action, p. 43 ("knowing the mechanism regarding lymphocyte antibody production is helpful but in and of itself does not preclude obviousness and particularly a reasonable expectation of success, since absolute certainty is not required; and knowledge of mechanism is not always complete nor even known prior to practicing a claimed invention."). Moreover, the Office improperly fails to consider the complete picture provided to one of ordinary skill in the art in early April of 1983 by the cited prior art in the context of all relevant evidence of record. See W.L. Gore. v. Garlock, 721 F.2d 1540, 1550, 220 U.S.P.Q. 303, 311 (Fed. Cir. 1983) ("district court erred . . . in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand."). In particular, the Office fails to weigh properly the observations within Rice that raise questions and identify a need for further research to understand the results being reported. In short, Rice paints a very different picture to a person of ordinary skill in the art in early April of 1983 than what the Office asserts.

i. Rice Does Not Describe Co-expression of an Exogenous Heavy Chain and an Exogenous Light Chain Gene

A person of ordinary skill in the art, reading Rice in early April of 1983, would not have equated a showing of (a) expression of one exogenous light chain gene in a lymphoid cell expressing its endogenous heavy chain gene, with (b) a process in which two exogenous immunoglobulin chain genes were introduced and expressed in a single lymphoid cell. See, e.g., Rice Second Declaration, ¶¶ 27-28; Harris Second Declaration, ¶¶ 61-62; Botchan Declaration, ¶¶ 67-69; McKnight Declaration, ¶¶ 82-83, 90-91.

ii. Rice Would Not Be Viewed as Being Generally Extendable to Expression of Multiple Exogenous Genes in Lymphocytes or Other Host Cell Types

As Owners pointed out, by early April of 1983, immunoglobulin gene expression in lymphocytes was not well understood. What was known was that successful expression of immunoglobulin genes by lymphoid cells – as well as lymphoid cell viability – was influenced by many different factors. See, e.g., Rice Second Declaration, ¶¶ 11-16; Harris Second Declaration, ¶¶ 22-28, 51-53. Thus, evidence already provided by Owners demonstrated that:

- The timing and levels of expression of the endogenous heavy and light chain genes in the cell could affect expression of either chain. See, e.g., Rice Second Declaration, ¶¶ 12-13; Harris Second Declaration, ¶¶ 27, 52; Colman Declaration, ¶31.

- The unbalanced expression of the two immunoglobulin genes in a lymphoid cell could affect the production of the immunoglobulin polypeptides by that cell, as well as the subsequent folding, assembly, and secretion of the immunoglobulin tetramer, among other events. See, e.g., Rice Second Declaration, ¶¶ 14-15; Harris Second Declaration, ¶¶ 25, 27, 63; Colman Declaration, ¶¶ 31-32.

- The excess or unbalanced production of the heavy chain could prove toxic to hybridomas. See, e.g., Harris Second Declaration, ¶ 25; Rice Second Declaration, ¶ 14; Colman Declaration, ¶ 31.

- It was thought that expression of immunoglobulin genes and/or assembly of immunoglobulin molecules within a cell was dependent on the presence of one or more "helper" proteins, such as BiP. See, e.g., Harris Second Declaration, ¶ 26; Rice Second Declaration, ¶ 15; Colman Declaration, ¶¶ 33-34.

A person of ordinary skill in the art, equipped with this knowledge, would have expected these factors to be important, both as to cell viability and to the capacity of the cell to express the two immunoglobulin genes. See, e.g., Harris Second Declaration, ¶¶ 52-53.

The lack of knowledge, in early April of 1983, regarding how lymphocytes express immunoglobulin genes and subsequently assemble and secrete antibodies would not have led a person of ordinary skill in the art to extend the teachings in Rice as the Office asserts (e.g., by concluding that expression of exogenous heavy and exogenous light chains in a transformed lymphocyte would be successful).

Rice describes transfection of a particular lymphoid cell. Dr. Rice explained that this cell "was 'poised' to express an introduced exogenous light chain gene." Rice Second Declaration, ¶ 31. Even using that specialized host cell, Rice was unable to explain how to manage or address issues affecting expression of introduced immunoglobulin genes. For example, Rice indicates that expression of the reintroduced light chain gene might be under the control of the expression of the endogenous heavy chain gene. See Rice, p. 7865 ("The possibility that transcription of the light chain gene is controlled by a product of the heavy chain locus is an interesting possibility and needs further investigation."). This was consistent with the observations in the literature at that time suggesting a link between the expression of the two immunoglobulin genes, and protein

assembly and secretion. See, e.g., McKnight Declaration, ¶ 104; Colman Declaration, ¶¶ 31-32; Harris Second Declaration, ¶27. Rice also points out that expression of the introduced light chain gene was likely due to the presence of uncharacterized regulatory and control elements in the gene. See, e.g., Harris Second Declaration, ¶¶ 52, 54, 57, 58. In addition to not describing these apparently necessary regulatory and control elements, Rice did not provide an explanation of how they might be manipulated to facilitate expression of other exogenous immunoglobulin genes. See, e.g., Second Rice Declaration, ¶ 20; Harris Second Declaration, ¶ 54; Botchan Declaration, ¶66; McKnight Declaration, ¶ 83 All of these observations within Rice would have signaled uncertainty and an absence of necessary information – not predictability – to a person of ordinary skill in the art about achieving expression of even one exogenous immunoglobulin gene in a lymphoid cell. KSR, 82 U.S.P.Q. 2d at 1396-1397. That uncertainty would be even more pronounced for achieving expression of even one exogenous immunoglobulin gene in other types of host cells.

As such, one of ordinary skill in the art would not have had a reasonable expectation of successfully transfecting a host cell in the manner claimed by the 415 patent claims (i.e., with both (1) exogenous DNA encoding the light chain of an immunoglobulin and (2) exogenous DNA encoding the heavy chain of an immunoglobulin, and achieving expression of both sequences at controlled levels that would not kill the host cell) based on Rice.

iii. Dr. Baltimore's Views Do Not Address the Question of Obviousness

To counter this evidence, the Office cites the personal opinion of Dr. David Baltimore that "he and other (sic) working in the field would have expected that if two chains were expressed they would form a functional antibody" "without further testing of the idea" based on the "demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain . . ." As explained above in Section V(B)(6), the Office improperly relies on this third party opinion to support its views concerning Rice, as the subject of this declaration testimony is not contained within the Rice publication (i.e., it is a hypothetical situation where two exogenous genes would be inserted into a lymphoid cell line).

As Dr. Rice explained, contrary to Dr. Baltimore's contentions, a person of ordinary skill in the art in early April of 1983 would not have made these types of assumptions about whether

exogenous heavy and light chain immunoglobulin genes even could be co-expressed in the specific cell line they used, much less whether they would result in assembly into a functional immunoglobulin. See Rice Second Declaration, ¶¶ 20, 26, 30 and 57. Owners note that the Office simply misses the point when it suggests that, because assembly of heavy and light chains having different specificities was observed in Rice, one would expect assembly of heavy and light chains into functional antibodies with the same specificity. The evidence cited by Owners has demonstrated that a person of ordinary skill would have had many reasons to doubt whether an extension of the Rice experiments to insert two different immunoglobulin genes in the lymphoid cell line would result in any expression of the introduced genes, much less a "proper" expression. Given the knowledge about the dependence on proper expression of the immunoglobulin genes that existed in early April of 1983, this person would not "expect" to see assembly of immunoglobulin – there simply were too many unknown variables at the time about what might influence this immunoglobulin assembly process in the lymphoid cell.

Dr. Rice also noted that there are no observations in the Rice paper concerning potential use of their experimental system for the production of immunoglobulins tetramers. See Rice Second Declaration, ¶¶ 32, 56. Instead, he explains that the paper was focused exclusively on the cellular mechanisms that control immunoglobulin gene expression. See Rice Second Declaration, ¶ 52. This observation is also consistent with Dr. Rice's recollection that Dr. Baltimore did not ever convey an opinion to him comparable to what Dr. Baltimore included in his declaration while Dr. Rice was working in Dr. Baltimore's lab. See Rice Second Declaration at ¶ 54.

Dr. Botchan echoes these points in paragraph 70 of his declaration. See also McKnight Declaration, ¶¶ 89-90. As he explains:

> In addition, I believe the reported association of the exogenous light chain gene expression product with the endogenous heavy chain gene in the Rice paper would not have created broader expectations about immunoglobulin assembly, as the PTO states. In this respect, I disagree with the PTO's interpretation of Dr. Baltimore's declaration at page 53 of the Office Action. Dr. Baltimore states his expectation that "if two [immunoglobulin] chains were expressed [in the same mammalian cell], they would form a functional antibody." What Dr. Baltimore carefully avoids stating is whether he believed at the time it would have been

possible to successfully transform and express exogenous heavy and light chain genes in a mammalian cell line. Botchan Declaration, ¶ 70.

iv. Conclusions Regarding Rice

In sum, Rice does not even vaguely suggest that one could extend its experimental results to a setting involving expression of exogenous heavy and light chain genes in a single host cell. See, e.g., Rice Second Declaration, ¶¶ 32, 55-56; Harris Second Declaration, ¶¶ 57-62; Botchan Declaration, ¶¶ 67,72; McKnight Declaration, ¶¶ 87, 91. And, as numerous scientists have indicated, given the uncertainty expressed in Rice as to what factors contributed to the "successful" expression of the reintroduced recombinant light chain gene, one of ordinary skill in the art would not have reasonably expected successful introduction of two exogenous immunoglobulin genes into the same host cell or successful expression of both sequences.

Rice, like Axel, does not provide any information beyond what is implicit in the '567 patent claims (i.e., expression of one exogenous DNA sequence encoding one immunoglobulin light chain polypeptide in one transformed host cell). See, e.g., Harris Second Declaration, ¶ 66. Thus, Rice, like Axel, would not have suggested to, or motivated, a person of ordinary skill to modify the '567 patent claims to independently express exogenous DNA sequences encoding both an immunoglobulin light chain and an immunoglobulin heavy chain in a single co-transformed host cell followed by assembly of the expression products into a properly formed immunoglobulin molecule or fragment. See, e.g., Harris Second Declaration, ¶ 67; Rice Second Declaration, ¶ 30. Thus, contrary to the Office's assertions, a person of ordinary skill in the art would not have considered the teachings of Rice as providing any motivation or suggestion to modify the '567 claims to yield the subject matter of the '415 claims.

c. Kaplan Does Not Teach or Suggest Co-Expression of Heavy and Light Chains in a Single Host Cell

Read properly, Kaplan describes a procedure in which individual heavy or light immunoglobulin chains are to be produced in separate cell cultures, purified, and then combined in vitro to form an immunoglobulin. See, e.g., McKnight Declaration, ¶ 92; Botchan Declaration, ¶¶ 76, 77; see also Harris First Declaration, ¶¶ 40-41; Harris Second Declaration, ¶ 68. As Dr. Harris explains, a person of ordinary skill in the art in early April of 1983 would not have read Kaplan as suggesting or teaching that exogenous immunoglobulin heavy and light

chain genes should be expressed in a single bacterial host cell. See Harris Second Declaration, ¶ 70; see also Botchan Declaration, ¶ 77; McKnight Declaration, ¶ 96. As such, Kaplan adds nothing to what is already inherent to the '567 patent claims (i.e., production of individual immunoglobulin chains in separate host cells) and would provide no suggestion or motivation to modify these claims to yield the embodiments claimed in the '415 patent.

Despite this clear evidence, the Office asserts on page 55 of the February 2007 Office Action that

> although Kaplan fails to specifically exemplify the recombinant making of antibodies, Kaplan nevertheless provides a roadmap to one of ordinary skill in the art as to how to do so. Thus, the teaching of Kaplan is not limited to dependent claims drawn to the use of hybridomas, plasmids or host cells (as implied by the patentee), but is additionally relevant regarding enabling the suggestive teaching of the other references regarding co-expressing light and heavy chains in a host cell (prokaryotic, eukaryotic or otherwise) to obtain an assembled antibody capable of binding its corresponding antigen.

(emphasis added).

The Office's conclusions regarding Kaplan are difficult to decipher. To the extent that the Office is asserting that Kaplan is providing a "roadmap" to co-expression of heavy and light immunoglobulin chains in a single host cell, the Office is simply incorrect. Kaplan, as explained by Drs. Botchan, McKnight, and Harris, does not describe or provide any suggestion that heavy and light immunoglobulin chains should be produced together in a single transformed host cell. See, e.g., Botchan Declaration, ¶¶ 74, 77; McKnight Declaration, ¶ 96; Harris Second Declaration, ¶¶ 69, 70. Instead, Kaplan's road map is analogous to that in the '567 patent claim – it relates to production of only one immunoglobulin chain in each host cell.

To the extent that the Office is simply observing that Kaplan is providing information regarding sources of mRNA encoding individual human immunoglobulin chains that can be used in the presently claimed methods, the Office is correct. Kaplan does describe procedures for producing human hybridomas, which can be used as a source of mRNA encoding human immunoglobulin chains. This, however, is immaterial and irrelevant to the question of whether Kaplan provides any motivation to modify the '567 claimed procedures to yield the co-expression embodiments claimed in the '415 patent. Kaplan plainly does not.

d. Dallas Would Not Have Provided Motivation to a Person of Ordinary Skill in the Art to Modify the Procedures of the '567 Claims Taken in View of Axel, Rice, and/or Kaplan

The Office maintains its assertions that Dallas provides a specific suggestion to modify the combined teachings of the '567 patent claims, taken in view of Axel, Rice, and Kaplan. In particular, the Office asserts:

> . . . *Dallas* teaches that two different proteins (in addition to a selectable marker) can be expressed in a single host cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins.

February 2007 Office Action, p. 56.

The Office vastly overstates the actual teachings of Dallas. Moreover, in concluding that Dallas would have motivated a person of ordinary skill in the art to modify the '567 claims to achieve co-expression of both the light and heavy immunoglobulin chains in a single host cell, the Office improperly disregards the § 1.132 declaration evidence provided in Owners' prior response. These declarations explain why a person of ordinary skill in the art would not have turned to Dallas for – or found within it – information that would be relevant to co-expression of two complex eukaryotic proteins in a variety of host cell types. See, e.g., Harris Second Declaration, ¶¶ 71-78; Rice Second Declaration, ¶¶ 41-43. Drs. Botchan and McKnight agree that a person of ordinary skill in the art would not have found any motivation or guidance from Dallas relevant to co-expression of heavy and light immunoglobulin chains in a single host cell. Botchan Declaration, ¶¶ 78, 82, 83; McKnight Declaration, ¶¶ 97, 100, 101.

Rather than teach generally that "two different proteins . . . can be expressed in a single host cell," as the office asserts, Dallas actually shows only that one can transform a bacterial cell with two or more bacterial genes. As Dr. Harris previously explained, this was not a significant experimental conclusion, but was instead similar to what was known by the late 1970's; namely, that one could transform bacterial cells with exogenous bacterial genes. Dr. Harris, for example, compared this showing in Dallas to transformation of bacterial cells with two antibiotic resistance genes (e.g., which are also bacterial genes). Harris Second Declaration, ¶ 73.

Dallas, thus, was not the broadly insightful demonstration that the Office suggests it was (i.e., that it would teach and motivate one of ordinary skill in the art to predictably produce and recover multiple complex mammalian proteins from one bacterial cell, or that these bacterial gene expression procedures would be relevant to expression of one or more mammalian proteins in any type of host cell). As the submitted evidence demonstrates, to a person of ordinary skill in the art in early April of 1983, Dallas would not have provided any relevant insights concerning production of two complex eukaryotic proteins in a single transformed bacterial host cell because of its focus on expressing genes encoding small bacterial antigens. See Botchan Declaration, ¶ 78; Harris Second Declaration, ¶¶ 71, 72. Similarly, as evidence of record establishes, Dallas would have provided no guidance or suggestion to a person of ordinary skill concerning expression of one or more proteins in a single eukaryotic cell, such as a mammalian cell line or the lymphoid cell line discussed in Rice. See Botchan Declaration, ¶¶ 78-83; McKnight Declaration, ¶¶ 97-102, Rice Second Declaration, ¶ 42, Harris Second Declaration, ¶¶ 72, 73.

Moreover, Dallas expressly teaches that the expression product(s) of the introduced bacterial genes are not to be recovered from the transformed host cell. Harris Second Declaration, ¶ 76. Indeed, as § 1.132 declaration evidence explains, in order for the Dallas vaccine to be useful, the expressed bacterial antigens must remain associated with the transformed bacterial cell. Id. This fact provides further support for the declarants' conclusions that a person of ordinary skill in the art would not have viewed Dallas as making the '415 patent claims obvious or predictable, given the ultimate goal of the '415 claims of recovering immunologically functional molecules or immunoglobulin fragments.[18]

The Office's simplistic analysis of Dallas is inconsistent with how a person of ordinary skill in the art, in early April of 1983, would have viewed the disclosure in Dallas, considered alone and in conjunction with Axel, Rice, Kaplan, and the '567 patent claims. The Office also ignores the different objective of the Dallas experiments, W.L. Gore, 721 F.2d at 1550, 220 U.S.P.Q. at 311, particularly that the "Dallas procedures explicitly do not isolate these proteins from the bacterial hosts" (McKnight Declaration, ¶ 98), compared to claim 1 of the '567 patent, which requires "recovering the chimeric heavy or light chain from the host cell culture." As

[18] Recovery of the produced chimeric heavy or light immunoglobulin chain is also required by the '567 patent claims. See, e.g., '567 patent, claim 1.

such, Owners submit that Dallas would not have provided the guidance or motivation that the Office finds, alone or in combination with Axel, Rice, and/or Kaplan to modify the '567 claims to yield the '415 claims. Owners respectfully request withdrawal of the rejection of claims 1-36 of the '415 patent in view of the '567 patent, taken in view of any of Axel, Rice and/or Kaplan, and taken further in view of Dallas.

2. The Deacon, Valle 1981, and Ochi References Would Not Provide a Further Motivation or Suggestion to Produce an Immunoglobulin Molecule or Immunologically Functional Fragment Using the Claimed Processes and Methods.

The Office asserts that Deacon, Valle 1981, and Ochi "provide further motivation to perform the Cabilly 1 patented steps in a single cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering the production of a functional antibody with a reasonable expectation of success." February 2007 Office Action, p. 36 (emphases added). As explained in Owners' prior response, however, a person of ordinary skill in the art in early April of 1983 would not have equated the experimental results observed in the Xenopus oocytes mRNA microinjection experiments, as reported in Deacon and Valle 1981, to genetically transformed host cells in light of the unique qualities of oocytes. As for Ochi, the Office's analysis suffers from similar flaws to its analysis of Axel, Rice, and Kaplan; namely, it fails to appreciate that Ochi describes an experiment where only one exogenous light chain gene was used to transfect a cell line and ignores the uncertainty observed within Ochi about achieving even this limited outcome. Contrary to the Office's assertions, a person of ordinary skill would not have read Ochi as providing a suggestion or motivation to insert two different types of exogenous DNA chains.

a. The Teachings in Deacon and Valle 1981 Are Greatly Limited and Would Not Set Expectations Concerning Transformed Host Cells

As with other prior art references, the Office overstates the teaching of Deacon and Valle 1981 to reach its obviousness position. In particular, the Office contends that these references simply introduce exogenous light and heavy chains (mRNA of each) into a eukaryotic cell (Xenopus oocyte) and achieve assembled functional immunoglobulins. See February 2007 Office Action, pp. 35-36

Owners refer the Office to the opinions of Drs. Harris, Rice, McKnight, and Botchan concerning these publications. See Harris Second Declaration, ¶¶ 87-97; Rice Second Declaration, ¶ 45; McKnight Declaration, ¶¶ 103-108; Botchan Declaration, ¶¶ 84-94. As these experts explain, the Deacon and Valle 1981 references describe experiments which use an mRNA fraction isolated from a lymphocyte that is successfully producing an immunoglobulin – indicating that the lymphocyte had all the genetic information necessary to transcribe its endogenous genes coding for the heavy and light immunoglobulin chains. See Harris Second Declaration, ¶ 95; Colman Declaration, ¶¶ 15, 30; McKnight Declaration, ¶ 105; Botchan Declaration, ¶ 91. As described in Deacon and Valle 1981, the mRNA preparations are purified to varying degrees, and then physically injected into the cytoplasm of Xenopus oocytes.

The Office's "reasonable expectation of success" conclusion is predicated on the following three positions:

- a Xenopus oocyte is a "host cell" within the meaning of the '415 patent, see February 2007 Office Action, p. 36.
- production of immunoglobulin tetramers via microinjection of Xenopus oocytes with mRNA fractions, as opposed to transforming host cells with vector DNA as in the '415 patent claims, would have been viewed by a person of ordinary skill in the art as a distinction without substance in early April of 1983, id., pp. 35-36, 63.
- the experimental results reported in Deacon and Valle 1981 would establish to a person of ordinary skill in the art that it was reasonably likely that functional immunoglobulin would be formed in any type of eukaryotic cell transformed with exogenous DNA sequences encoding immunoglobulin heavy chain and light chain polypeptides (i.e., that the formation of immunoglobulin tetramers in any cell would have been predictable based on the Xenopus experiments), id., pp. 62-63.

As detailed below and as evidenced in prior § 1.132 declaration evidence, each of these positions are scientifically flawed and unsupported. Owners previously provided § 1.132 declaration evidence from Dr. Alan Colman. Dr. Colman is a recognized expert in the use of the Xenopus oocyte experimental translation system, and was the principle investigator of the work that was reported in the two Valle publications. Dr. Colman is clearly qualified to provide an explanation of what the views of a person of ordinary skill in the art would have been in early April of 1983 concerning the Xenopus oocyte work described in Deacon and Valle 1981. Owners also refer the Office to the opinions of Drs. Harris, Rice, McKnight, and Botchan

concerning these publications. See Harris Second Declaration, ¶¶ 87-97; Rice Second Declaration, ¶ 45; McKnight Declaration, ¶¶ 103-108; Botchan Declaration, ¶¶ 84-94. These experts share the views of Dr. Colman, and illustrate why the Office's conclusions are incorrect.

i. A Xenopus Oocyte Is Not a "Host Cell" Let Alone a Transformed Host Cell

The claims of the '415 patent require not just use of a "host cell" but of a host cell that has been transformed with exogenous DNA sequences. The Office overlooks this and other critical distinctions between the Xenopus oocytes that were the subject of the Deacon and Valle 1981 publications and the subject matter of the '415 patent claims to erroneously reach its conclusions regarding what a person of ordinary skill in the art would have reasonably expected from the work described in these papers relative to what is required by the '415 patent claims.

First, as Dr. Colman observed, "[b]ecause an oocyte cannot replicate, it cannot function as a host cell as I understand the meaning of that term from the '415 patent." Colman Declaration, ¶ 19. Dr. Colman also explained why a person of ordinary skill in the art would not equate a Xenopus oocyte with "the types of 'differentiated' mammalian cells (in addition to cell types such as bacteria and yeast cells) that the patent indicates are suitable as host cells." Colman Declaration, ¶ 20.

Second, he explained that a Xenopus oocyte is not transformed with DNA pursuant to the experiments in Valle 1981 and Deacon, and will have no "progeny" that contain "genetic information" related to the mRNA that is injected into the Xenopus oocyte cell. See Colman Declaration, ¶ 19; see also Harris Second Declaration, ¶ 92. These observations are confirmed by Drs. Botchan and McKnight. Botchan Declaration, ¶¶ 86, 93; McKnight Declaration, ¶ 105.

Thus, the § 1.132 declaration evidence submitted by Owners clearly explains why a person of ordinary skill in the art would not have considered a Xenopus oocyte, by any interpretation, to be a "host cell" within the meaning of the '415 and '567 patents, let alone a transformed host cell as required by the '415 patent claims. The Office cites nothing to counter this evidence, other than to provide its own reading of a passage from the '415 specification. See

February 2007 Office Action, p. 17.[19]. Plainly, the Office's conclusion that a Xenopus oocyte is a host cell is an unsupported conclusion and is directly contrary to the § 1.132 declaration evidence of qualified experts. In re Ziedler, 682 F.2d at 967, 215 U.S.P.Q. at 494; In re Katzschmann, 347 F.2d at 622, 146 U.S.P.Q. at 68. This significant error renders their conclusions based on it improper and scientifically inaccurate

ii. The Differences Between Translation of mRNA in a Xenopus Oocyte and Production of Immunoglobulin Chains by Transformed Host Cells Are Significant

Unlike the Office, a person of ordinary skill would have considered the differences between translation of mRNA extracts in a Xenopus oocyte and production of an immunoglobulin by a host cell transformed with DNA encoding heavy and light chains to be very significant in early April of 1983.

The evidence of record demonstrates that a person of ordinary skill in the art in early April of 1983 would have immediately appreciated that the Xenopus oocyte has unique characteristics relative to other types of cells that would cause that person to not have the opinions expressed by the Office. See Colman Declaration, ¶¶ 21-24. These unique features (e.g., enormous size, which permits unique physical manipulations; tolerance of extreme physical manipulation; highly promiscuous translational capacity; extended viability) made the Xenopus oocyte a very useful experimental tool. See Colman Declaration, ¶¶ 21-22; Harris Second Declaration, ¶ 91. See also Botchan Declaration, ¶ 87. But, as Dr. Colman explains, the experimental results obtained in Xenopus oocytes would not have been viewed by those of ordinary skill in the art as being representative of what might be observed in host cells according to the '415 patent. See Colman Declaration, ¶¶ 24, 25; See also Harris Second Declaration, ¶¶ 90-93; McKnight Declaration, ¶¶ 105, 107-108; Botchan Declaration, ¶¶ 93-94.

For example, Dr. Colman explains in paragraph 15 of his declaration that:

> . . . [T]he *Xenopus* work described in *Valle 1981* and *Deacon* does not answer significant questions that existed in early April of 1983 regarding assembly and secretion of immunoglobulins by mammalian cells. These questions involved issues such as how to control the timing of expression

[19] Owners also observe that the Office has ignored in its analysis the requirement that the host cell be "transformed."

> of the immunoglobulin genes, how to control the levels of such expression, the role of "molecular chaperone" proteins in the folding, assembly and secretion of the immunoglobulin, among other issues.

See also Harris Second Declaration, ¶ 93 (finding that there were "substantial differences between 'host cells' and Xenopus oocytes that would have been known by a person of ordinary skill in the art in early April of 1983"); McKnight Declaration, ¶ 105.

Similarly, as Dr. Botchan explains:

> The mRNA found in the cytoplasm of cells that proliferate is limited to mRNA that is actively being translated. In such cells – for example, differentiated host cells – mRNA is present in the cytoplasm only transiently, and only during the active translation of the message into protein. *See, e.g.*, Ross, *Microb. Rev.* 59(3): 423-450 (1995). This cellular environment is not at all analogous to the environment of the *Xenopus* oocyte, where large amounts of mRNA are stored in the cytoplasm, translation of the stored mRNA has been suppressed, and components of the protein translation machinery (e.g., ribosomes) are abundant.
>
> Microinjection experiments in *Xenopus* oocytes do not result in a cell that replicates the cellular environment of a host cell that is translating an mRNA transcribed from integrated DNA. In the microinjection experiment, a very high local concentration of mRNA is injected into a compartment of the oocyte that is prepared to receive and translate the mRNA. In a cell producing protein after transcription of a gene, a very different pathway and a very different cellular environment is observed.

See Botchan Declaration, ¶¶ 88, 89. In other words, the setting within a Xenopus oocyte cell in which the heavy and light chain mRNA transcripts are being translated is very different than the environment of a host cell transformed with exogenous DNA sequences as required by the '415 patent claims. That is the oocyte setting presents a unique opportunity for the oocyte cell to translate an unusually large amount of mRNA encoding each chain within the cell in a precise manner, thereby sidestepping issues of controlled timing and levels of expression of DNA sequences within the nucleus of a transformed cell. As the § 1.132 declaration evidence of record establishes, this is a distinction that a person of ordinary skill in the art would have understood to be important and very significant, both as to host cell viability and to the capacity of the host cell to successfully express the introduced DNA sequences encoding the light and heavy immunoglobulin chains. And because the Deacon and Valle 1981 papers do not provide

any information regarding how to manage or address issues affecting expression of introduced DNA sequences in transformed host cells the results observed in the Xenopus oocyte setting would not have been considered by one of ordinary skill in the art to make predictable the co-expression of exogenous immunoglobulin heavy and light chain DNA in a host cell. Colman Declaration, ¶¶ 33, 35; Botchan Declaration, ¶¶ 91-92; McKnight Declaration, ¶ 105. In sum, Deacon and Valle 1981 do not provide any answers that would be relevant to the transformation of a host cell with DNA or the production within that host cell of heavy and light chains of an immunoglobulin.

iii. A Person of Ordinary Skill in the Art Would Not Have Extrapolated the Results Concerning Assembly of Immunoglobulins in Xenopus Oocyte mRNA Experiments to Transformed Host Cells

The Office also takes the position, based on its reading of Valle 1981 and Deacon, that the demonstration of translation of mRNA transcripts encoding heavy and light chains followed by immunoglobulin assembly would have led a person of ordinary skill in the art to expect, in early April of 1983, that the same result would be observed in a host cell transformed with DNA encoding heavy and light chains. This conclusory statement stands in stark contrast to the § 1.132 declaration evidence of Drs. Colman, Harris, and McKnight that clearly explain why the Office's conclusions are scientifically incorrect. Their explanations make clear that a person of ordinary skill in the art would have considered the microinjection of mRNA fractions into a Xenopus oocyte to be a substantially different undertaking than transformation of a host cell with exogenous DNA sequences. As such, they have explained why a person of skill in the art would not have reasonably expected to achieve the "same" outcome (i.e., assembly of heavy and light chains into an immunoglobulin molecule). The § 1.132 declaration evidence calls into question the basis and accuracy of the Office's conclusions.

One significant difference is that "the oocyte experiments employ messenger RNA (mRNA) which has been extracted from cells specialized for, and which actually are producing, functional immunoglobulin." Colman Declaration, ¶¶ 15, 30; see also Harris Second Declaration, ¶ 95; McKnight Declaration, ¶ 105. Dr. Harris explains that "mRNA is itself the product of the expression of genes or an introduced DNA sequence by the transcriptional processes of the cell." See Harris Second Declaration, ¶ 95; see also McKnight Declaration, ¶

107 ("mRNA is not equivalent to DNA in its function or role in a cell."); Botchan Declaration ¶ 92 ("I believe the PTO fails to appreciate the significant difference between 'using vector DNA' for 'host transformation' and microinjecting mRNA – which does not result in 'host transformation' of the *Xenopus* oocyte."). As Dr. Colman succinctly explains (at paragraph 30 of his declaration):

> By using products of a successful transcription of the immunoglobulin genes, one can bypass the challenge of constructing an appropriate DNA construct with the necessary control and other regulatory elements to (i) successfully transform a host cell and enable transcription of the exogenous immunoglobulin genes, and (ii) achieve the correct balance of heavy and light chain transcripts so that excess expression of heavy chains does not occur.

The shortcuts in Deacon and Valle 1981 leave unanswered many significant questions. As such, Deacon and Valle 1981 cannot be accurately portrayed as providing guidance to a person of ordinary skill in the art as to how to achieve co-expression of exogenous DNA encoding heavy and light chain polypeptides, much less as providing a basis for a reasonable expectation by such a person that immunoglobulin assembly will ensue from any expression of the two chains by a transformed host cell. See Colman Declaration, ¶¶ 15, 30.

iv. The Statements in the European Patent Office Opposition Proceedings Are Irrelevant and/or Inadmissable in the Present Reexamination Proceedings

The Office, despite the evidence presented in the § 1.132 declarations, asserts that Owners have made "admissions" that foreclose it from contesting the scientific accuracy of the Office's assertions (i.e., that a person of ordinary skill in the art would view the results in Deacon and Valle 1981 as demonstrating that "expression of an immunoglobulin in an undifferentiated eukaryotic host cell (i.e., Xenopus oocyte) would be correlative to a host cell within the scope of the instantly claimed invention.") In particular, the Office points to a statement contained in a document filed by the legal representative of one of the Owners in a European Patent Office opposition proceeding. The Office misreads the statement, improperly gives it "admission" status, and ignores applicable law and Office practice regarding "admissions."

The Office's reliance on the statement as an admission is improper because it is not an admission as to a fact, but mere attorney argument. Pursuant to M.P.E.P. § 2145, attorney

argument cannot take the place of evidence in the record. M.P.E.P. § 2145, citing In re Schulze, 346 F.2d 600, 602, 145 U.S.P.Q. 716, 718 (C.C.P.A. 1965); In re Geisler, 116 F.3d 1465, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997).

The statement cited by the Office is plainly not a factually correct statement. For example, as Dr. McKnight explains, the statement in the pleading that Valle "clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected with separate DNA molecules encoding its heavy and light chains respectively" is factually incorrect. McKnight Declaration, ¶ 107. As he points out, Valle 1981 (and Valle 1982) did not use DNA in their experiments, but mRNA. He also explains that the hypothesis that mRNA is "functionally equivalent" is factually incorrect, as a scientific matter, given that mRNA has the function of facilitating translation of genetic information into polypeptide sequences, while DNA has the function of storing genetic information for passage to progeny of the cell. McKnight Declaration, ¶¶ 107-108.

The content of the statement also cannot support the assertions set forth by the Office at page 64 of the Office Action. As Owners have explained, a Xenopus oocyte is not a host cell within the meaning of the '415 patent. Similarly, any assertion that it is a host cell does not reflect scientifically accurate views of a person of ordinary skill in the art. The person who made the statement in the European proceeding was a European patent agent, not a person of ordinary skill in the art.

Since an attorney's statement cannot change the truth or falsity of a fact – and the statement in this case plainly is incorrect – it cannot be viewed as "evidence" that can displace the evidence of record in this case in the form of § 1.132 declarations from qualified experts. The Office cites this attorney statement as a counterweight to the extensive evidence of record, which is plainly improper under Office policy. Accordingly, the statement is neither a factual admission nor is persuasive to the factual issue being asserted by the Office (i.e., what the Deacon or Valle 1981 publications would have taught or suggested to a person of ordinary skill in the art in early April of 1983).

Finally, even if this factually erroneous attorney argument were to be considered an admission by one of the Owners, the M.P.E.P. prohibits use of such an admission, because it was

submitted by a third party in this ex parte reexamination proceedings. See M.P.E.P. § 2258(I)(F) ("A third party, however, may not submit admissions of the patent owner made outside the record. Such a submission would be outside the scope of reexamination.").

b. Ochi and Oi Would Not Have Set Expectations for Production of an Immunoglobulin from Host Cells Transformed with Exogenous Heavy and Light Chain DNA

Ochi would not have been read by a person of ordinary skill in the art in early April of 1983 as the Office suggests. See Rice Second Declaration, ¶¶ 33, 44; Harris Second Declaration, ¶ 86. This conclusion is explained below, and in the expert declarations by Drs. Rice and Harris. Ochi, like Axel, Rice, and Kaplan, does not provide any information beyond what is implicit in the '567 patent claims (i.e., expression of one exogenous DNA sequence encoding one immunoglobulin light chain polypeptide in a transformed host cell). See Harris Second Declaration, ¶ 86. Accordingly, Ochi does not provide any suggestion or motivation that would support a finding of obviousness-type double patenting, including with respect to assembly of exogenous heavy and light DNA chains into an active antibody.

Ochi, similar to Rice, describes an experiment where only one exogenous light chain gene was used to transfect a hybridoma cell line that was already expressing endogenous heavy chain genes and at least one light chain gene. See Harris Second Declaration, ¶¶ 80, 81; Rice Second Declaration, ¶¶ 34, 35. The mutant line did not express an endogenous anti-TNP light chain gene but did express its endogenous anti-TNP heavy chain gene, along with the heavy and light chain genes contributed to the hybridoma from the fusion partner. See id. Moreover, the Ochi work took advantage of unusual circumstances that effectively ensured that the experiment would be a success. The experiment tested the limited hypothesis that "one could restore gene expression in a cell line that, due to a random mutation, lost its ability to express the same gene." Harris Second Declaration, ¶ 83, citing Ochi, p. 340. It used cells that "normally permit immunoglobulin production" Id. In view of these unusual circumstances, Ochi would not have suggested to one of ordinary skill in the art that "their transfection and expression results would be broadly extendable to any type of cell line or situation." Id. Ochi did not attempt to transfect any cell with a heavy chain gene, or with both heavy and light chain genes. See Harris Second Declaration, ¶¶ 82-84.

The Office asserts that Ochi would have led a person of ordinary skill in the art to "reasonably expect" production of functional immunoglobulin in situations where a host cell (of any type) is transformed with DNA sequences encoding heavy and light chains. The evidence of record, including statements within Ochi, does not support the conclusions of the Office.

The probative value of Ochi is also severely limited by the authors' acknowledgement that they were unable to explain how the transformed hybridoma cells were able to produce the results they observed. See Harris Second Declaration, ¶ 85; Rice Second Declaration, ¶ 36. Dr. Rice explains that Ochi identifies several areas of uncertainty regarding the expression of immunoglobulin genes in lymphocytes despite its relatively simple experimental model, including varying levels of expression and confusion over the factors that triggered expression of the light chain gene. Rice Second Declaration, ¶¶ 35, 36. Dr. Rice, a person with relevant experience in the field of the Ochi experiments, explained that a person of ordinary skill would not attach much significance to the Ochi results, particularly not the significance attached by the Office. As he explains at paragraph 37 of his second declaration:

> Even though the experimental design of the *Ochi* work seems relatively straightforward in hindsight (*i.e.*, restoring lost expression of a light chain gene), their results were considered significant enough to be published in *Nature*, which at the time was, and still is, considered to be one of the most prestigious peer-reviewed scientific journals in the world. This shows how non-routine expression of even a single exogenous immunoglobulin gene was in early April of 1983.

Similarly, Dr. Harris explained that "a person of ordinary skill in the art would not broadly extend the observations and findings in the Ochi paper as the Office suggests," namely as something that provides motivation or suggestion to modify the '567 claimed embodiment to yield those claimed in the '415 patent. Harris Second Declaration, ¶ 84. See, infra, section V(D)(I)(b)(iii).

Accordingly, because of the extremely limited nature of the experiment described in Ochi, and in view of the observations in the paper that raised significant questions about the results being reported, a person of ordinary skill in the art would not share the views of the Office that Ochi provides any reasonable basis for extrapolating its results to any setting where host cells would be transformed with multiple exogenous immunoglobulin genes.

3. The Addition of the '545 Patent to the String of References Relied Upon In Section Seven of the Office's Analysis Does Not Remedy the Deficiencies in the Office's Analysis

The Office reasons that the Moore '545 patent provides further motivation to advance from the '567 patent claims to the '415 patent claims, particularly with respect to co-expression of light and heavy antibody chains. As detailed above in, however, the claims of the more '545 patent are not prior art under § 102(e) to the '415 patent, and can thus not be considered prior art for purposes of an obviousness-type double patenting analysis. Moreover, the specification of the '545 patent does not describe in any way co-expression of light and heavy chain variable region polypeptides in a single host cell. As such, the relevant aspects of the '545 patent for an obviousness-type double patenting analysis fail to teach anything relating to co-expression of light and heavy immunoglobulin chains in a single transformed host cell. As such, it would provide no motivation or suggestion to a person of ordinary skill in the art when combined with the '567 patent claims, Axel, Rice, Kaplan, Dallas, Ochi, Oi, Deacon, and/or Valle 1981.

E. The Office's Rejection of the Dependent Claims Is Not Supported by the Cited References.

The Office cites various publications for disclosures it believes are relevant to certain dependent claim limitations. The Office's reasoning and analysis for the rejection of each of the dependent claims are superficial and dependent on its reasoning for the claims upon which these claims depend. Accordingly, Owners' responses to these rejections are consequently limited. The discussion below follows the order and groupings in which the claims are treated at pages 37-42 of the February 2007 Office Action.

1. Claim 5

The Office notes that the claims of the '567 patent do not require the use of a pBR322 vector, and then identifies a reference that involves pBR322. In particular, the Office cites Axel and Kaplan for the teaching that pBR322 is a plasmid that is useful for expressing heterologous proteins. Based on this teaching, the Office concludes that the invention of instant claim 5 is obvious.

Neither of these references teaches that pBR322 is particularly suitable for expressing DNA sequences encoding immunoglobulin heavy and light chain polypeptides in a single

transformed host cell, which is the content of claim 5. Accordingly, these references, alone or together, do not provide motivation to modify the base claims to arrive at the process in claim 5. Consequently, the Office's finding of obviousness-type double patenting with respect to this dependent claim is unsupported.

2. Claims 6-8, 19, 20, and 26

The Office states that claims 6-8, 19, 20, and 26 differ from the claims of the '567 patent in "using bacterial/yeast/mammalian host cells including E. coli strain X1776." The Office thus agrees that none of the claims of the '567 patent requires any of these specific host cell types. The Office then begins listing references that involve some, but not all (i.e., X1776), of these types of host cells, and proceeds in a conclusory fashion to find that those references help establish obviousness with respect to the above-referenced claims.

The Office cites Axel and Rice for teaching the use of mammalian host cells. Axel and Rice simply do not describe any co-expression strategy aimed at producing two or more proteins of interest. See Harris Second Declaration, ¶¶ 35-48. Thus, neither Axel nor Rice describe or suggest particular cell lines that would be suitable for the co-expression of heavy and light chain immunoglobulin polypeptides as required by claims 6-8, 19, 20, and 26.

The Office states that Kaplan teaches that bacteria and yeast cells can be used as host cells for producing immunoglobulin chains. However, Kaplan does not teach or suggest that any host cell should be used for co-expressing heavy chain and light chain genes, as Dr. Harris explains in his Second Declaration at ¶¶ 68-70. Nothing in Kaplan would reasonably lead one of ordinary skill to expect that these microbial host cells would be useful in a co-expression process.

Finally, none of Axel, Kaplan, and Rice even identifies E. coli X1776, let alone teaches why it would be useful for any particular purpose. The Office has identified no evidence in the prior art that is even marginally relevant to the use of this particular host cell type according to the claimed invention.

Because the cited references do not supply any reason, motivation, or expectation of success for using various host cell types according to the methods of claims 6-8, 19, 20, and 26, they do not support a prima facie case of obviousness-type double patenting.

3. Claims 9 and 29

The Office recognizes that claims 9 and 29 differ from the claims of the '567 patent in that they require the secretion of a functional antibody protein from a host cell, a feature which is not recited or required by the '567 patent claims. In an attempt to bridge this gap, the Office relies on the generic disclosure of mammalian host cells in Axel and on the description of cells that express introduced light chain polypeptides in Rice. Neither reference, however, states or suggests anything about the secretion of functional antibodies by mammalian host cells transformed with DNA encoding heavy chain and DNA encoding light chain immunoglobulin polypeptides.

Axel, as noted above, merely describes certain mammalian host cells that are suitable for use in conjunction with its basic marker gene technology. Also, because Axel does not address co-expression of two polypeptides of interest – such as an immunoglobulin heavy and an immunoglobulin light chain polypeptide – it similarly does not address production and secretion of a functional immunoglobulin molecule or fragment.

As Dr. Rice explains in his First Declaration, the experiments described in Rice are not capable of producing any functional antigen-binding antibody molecules because the endogenous heavy chain does not have the same antigen binding specificity of the exogenous light chain gene used to transfect the cell line. See Rice First Declaration, ¶¶ 11, 16. See Rice Second Declaration, ¶ 17. Thus, Rice contains no teaching or suggestion that would lead one of ordinary skill to prepare any type of host cell, transformed or otherwise, with the expectation that it would be useful for preparing secreted, functional antibody tetramers.

As neither Axel nor Rice specifically suggests production of an immunoglobulin molecule or a functional fragment via secretion by a transformed host cell, these references do not support a prima facie case of obviousness-type double patenting as to claims 9 and 29.

4. Claims 10 and 27-32

The Office states that claims 10 and 27-32 require further limitations involving expression of insoluble immunoglobulin polypeptides, solubilization of such polypeptides, and refolding of the solubilized polypeptides to produce functional antibody molecules. The Office acknowledges that the claims of the '567 patent do not require limitations that correspond to claims 10 and 27-32 of the '415 patent.

The Office cites Kaplan and Builder as being relevant to expression and solubilization of immunoglobulin polypeptides in host cells such as E. coli. Kaplan, however, does not teach or suggest that any host cell should be transformed with first and second DNA sequences encoding immunoglobulin heavy and light chains, and it does not address expression, solubilization, or refolding of immunoglobulin heavy and light chain polypeptides to produce an immunologically functional immunoglobulin. Builder provides disclosure that is relevant to the generic problem of refolding recombinant polypeptides, but it contains no specific suggestion regarding refolding compositions containing constituent polypeptides of a multimeric protein that have been independently produced in a cell, such as is required by the claims of the '415 patent. See, e.g., Harris Second Declaration, ¶ 99.

Dr. Harris explains the structural complexity of an immunoglobulin tetramer. See Harris Second Declaration, ¶¶ 13-18. Particularly in view of his observations, the generic disclosure in the cited references cannot be said to provide any specific direction that makes any or all of claims 10 and 27-32 prima facie obvious in view of the claims of the '567 patent. Thus, neither Kaplan nor Builder, alone or together with any other references of record, suggests modifying the '567 claims so as to yield claims 10 and 27-32, and they, therefore, do not support the Office's finding of obviousness-type double patenting.

5. Claim 12

The Office notes that claim 12 of the '415 patent differs from the claims of the '567 patent as it requires the use of constant and variable domain DNA sequences corresponding to the same source antibody. Not only is this feature not recited in the claims of the '567 patent, it is specifically excluded from the claims of that patent because they require the production of chimeric antibody chains. Moreover, the Office cites no prior art evidence that indicates why a

method of making a tetrameric immunoglobulin molecule comprising a coding sequence having DNA from a single source would be an obvious modification of a method of making a single immunoglobulin polypeptide that is required to use DNA from different sources.

Because the Office has cited no evidence that addresses the further limitation of claim 12, it has not set forth a prima facie case of obviousness-type double patenting as to that claim.

6. Claim 14

Claim 14 requires the use of immunoglobulin DNA from a hybridoma source, a feature that, as the Office observes, is not recited or required by any claims of the '567 patent. The Office notes that Kaplan teaches that hybridomas may be sources of mRNA encoding antibody chains for recombinant expression. However, as discussed at length above, Kaplan does not teach or suggest recombinant expression of immunoglobulin heavy chain and light chain polypeptides in a single host cell. Thus, Kaplan does not provide evidence that supports the obviousness of the invention of claim 14 as a whole.

7. Claim 22

Claim 22 requires the production of the immunoglobulin heavy chain and light chain polypeptides of an anti-CEA antibody, a feature which is not recited in any of the claims of the '567 patent. The Office notes that Accolla describes anti-CEA monoclonal antibodies. Such disclosure, however, does not address the obviousness of the invention of claim 22 as a whole. Because Accolla does not teach or suggest producing antibodies directed against CEA or any other antigen in a transformed host cell system, that reference does not support a prima facie case of unpatentability. Consequently, Claim 22 is separately patentable over the claims of the '567 patent, and the Office's justifications for obviousness-type double patenting are without merit.

8. Claims 34-36

Finally, the Office discusses claims 34-36, which depend from various claims and require the further step of attaching the antibody or antibody fragment to a label or drug. This step is neither implicit in nor required by any claim of the '567 patent. The Office cites Kaplan for generic disclosure relating to the use of drug-conjugated or radiolabeled antibodies for therapy or diagnosis, and concludes without analysis that this reference supports a finding of obviousness-

type double patenting for claims 34-36. This generic disclosure, however, adds nothing to the deficient rationale advanced by the Office concerning the use of a transformed host cell for production of an immunoglobulin molecule. Thus, because Kaplan does not provide evidence that establishes that the inventions as a whole of claims 34-36 are obvious in view of the claims of the '567 patent, the Office's conclusion is improper.

VI. Conclusions

Owners respectfully submit that all issues raised by the Office in the outstanding Office Action have been fully addressed above. Moreover, in view of the foregoing remarks, Owners submit that claims 1-36 of the '415 patent are patentable over the prior art and are not unpatentable for reasons of obviousness-type double patenting over the claims of the '567 patent, considered alone or in the various combinations of prior art cited by the Office. In particular:

- Claims 1-7, 9-10, 14-18 and 21, 23-36 are not anticipated under 35 U.S.C. §102(e) by the Moore '545 patent.
- Claims 1-7, 9-10, 14-21 and 23-36 are not obvious under 35 U.S.C. § 103(a) in view of the Moore '545 patent. Nor are claims 1-7, 9-10, 14-21 and 23-36 obvious under 35 U.S.C. § 103(a) in view of the Moore '545 patent as applied against claims 1-7, 9-10, 14-18, 21 and 23-36 and further in view of Axel as applied against claims 19-20.
- Claims 1-7, 9-10, 14-18 and 21-36 are not obvious under 35 U.S.C. § 103(a) in view of the Moore '545 patent as applied against claims 1-7, 9-10, 14-18, 21, and 23-36 in further view of Accolla as applied against claim 22.
- Claims 1-7, 9-11, 13-18, 21 and 23-36 are not unpatentable for reasons of nonstatutory obviousness-type double patenting over claims 1-7 of the '567 patent and the Moore '545 patent.
- Claims 1-7, 9-11, 13-21 and 23-36 are not unpatentable for reasons of nonstatutory obviousness-type double patenting over claims 1-7 of the '567 patent and the Moore '545 patent as applied against claims 1-7, 9-11, 13-18, 21 and 23-36 and further in view of Axel as applied against claims 19-20.
- Claims 1-7, 9-11, 13-18 and 21-36 are not unpatentable for reasons of nonstatutory obviousness-type double patenting over claims 1-7 of the '567 patent and the Moore '545 patent as applied against claims 1-7, 9-11, 13-18, 21 and 23-36 and further in view of Accolla as applied against claim 22.

- Claims 1-36 are not unpatentable for reasons of nonstatutory obviousness-type double patenting over claims 1-7 of the '567 patent in view of Axel, Rice, Kaplan, Builder, Accolla, Dallas, Deacon, Valle 1981, and Ochi. Nor are claims 1-36 unpatentable for reasons of nonstatutory obviousness-type double patenting over claims 1-7 of the '567 patent in view of Axel, Rice, Kaplan, Builder, Accolla, Dallas, Deacon, Valle 1981, Ochi, and the Moore '545 patent.

Consequently, Owners respectfully request that the rejections of the claims be withdrawn, and that the Office proceed to issue a notice of intent to issue reexamination certificate affirming the patentability of claims 1-36 of the '415 patent.

Owners respectfully request that the Examiner with primary responsibility for this merged reexamination proceeding contact the undersigned to discuss any issues not resolved by the above response.

The Commissioner is hereby authorized to charge Deposit Account No. 18-1260 for any additional fees required in connection with the filing of this Response.

Respectfully submitted,

Date: May 21, 2007

By: _____
Jeffrey P. Kushan
Reg. No. 43,401

SIDLEY AUSTIN LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
PHONE: (202) 736-8000
FAX: (202) 736-8711

CERTIFICATE OF SERVICE

The undersigned hereby certifies that copies of this paper are being served by first class mail delivery on the date shown below to each of the following:

Lisa V. Mueller, Wood, Phillips, Katz, Clark & Mortimer, 500 West Madison Street, Suite 3800, Chicago, IL 60661.

Elliot M. Olstein, Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 5 Becker Farm Road, 2nd Floor, Roseland, NJ 07068.

SIGNATURE	PRINTED NAME	DATE
[signature]	David L. Fitzgerald Reg. No. 47,347	21 May 07